# Diagnostic strategies and surgical procedures for thoracic tumors

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# CONTENTS

## Chapter 8



## Chapter 9

# General introduction and aim of the thesis

In the Netherlands over 100.000 new cancer cases were diagnosed in 2015 and over 45.000 patients died because of cancer. It makes cancer the leading cause of death in the Netherlands. Over 12.000 (11%) new lung cancers were diagnosed of which over 10.000 died (88%). Lung cancer has a bad prognosis with an overall 5-year survival of 17%. (bron: kwf.nl). Worldwide, lung cancer is still the leading cause of cancer-related death with an overall 5-year survival at approximately 18% [1]. Tumors in the lungs can originate from the lung itself, so called primary pulmonary tumors, or can be metastases from other malignancies. Primary pulmonary tumors contribute to a large extent to the number of cancer related deaths as mentioned before.

Computed tomography (CT) of the chest, whole body positron emission tomography-CT (PET-CT) and magnetic resonance imaging (MRI) of the brain have improved radiological oncologic staging and have become an essential part of the evaluation of patients with suspected pulmonary tumors and mediastinal lymph nodes. However, these techniques cannot provide definitive tissue diagnosis and they are associated with low sensitivities (70%) and specificities (94%) [2-10]. Transthoracic lung biopsies, thoracoscopic wedge resections or biopsies as well as endoscopic ultrasound techniques allow to obtain tumor tissue for cytological and histological examination. However, despite improvements in these diagnostic procedures, the overall prognosis of patients with lung cancer remains poor [11,12] and depends on tumor size and presence or absence of metastases [13,14].

Precise staging is vital in determining cTNM stage to predict outcome [15-17]. In patients with potentially resectable oligometastatic disease, it is important to determine the overall metastatic burden: only a limited amount of metastases are appropriate for resection in case the primary tumor site is under control either by conventional radiotherapy or targeted therapy [18,19].

This emerging field of extending surgery for metastatic disease is still under investigation in a time in which immunotherapy and other targeted therapies increase control over selected patients with lung cancer. Cervical mediastinoscopy has proven to accurately select patients with Non-Small Cell Lung Cancer (NSCLC) for surgery, with a false negative rate of 8%-11% [20-22]. In 1959 the technique was first described by Carlens[23] and until recently cervical mediastinoscopy was considered to be the gold standard in mediastinal staging of NSCLC [22,24-28]. The role of the cervical mediastinoscopy is changing after the introduction of PET-CT and emerging endoscopic ultrasound techniques. However, cervical mediastinoscopy remains an important tool in

oncologic staging of the mediastinum with a sensitivity of 89% and specificity of 100% [29,30].

The novel endoscopic ultrasound techniques for mediastinal staging have now become the first diagnostic staging method in many centers. These endoscopic ultrasound techniques are far less invasive than mediastinoscopy and they are safe with a low morbidity. As endoscopic ultrasound techniques can only provide cytology, this is one of the drawbacks of these techniques. Also, representative specimens depend strongly on the operator as well as on the judgment of the cytologist who examines the specimens. This is especially the case in ROSE, Rapid Onsite Specimen Examination[31].

Cervical mediastinoscopy is also a complex technique and thus it is operator dependent in how adequate the specific mediastinal lymph node stations can be biopsied [32]. An important issue in both techniques is the number of surrounding mediastinal lymph node stations that can be biopsied. The extent of the mediastinal exploration is inversely related to the chance to miss mediastinal metastases. The adequacy of endoscopic ultrasound techniques as well as cervical mediastinoscopy strongly depends on the experience of the operator [33-35].

In **CHAPTER 2** we hypothesized that the success of a cervical mediastinoscopy was dependent on the operator experience, patient related restrictions and video-mediastinoscopy.

**CHAPTER 3** discusses the 'rise and fall' of cervical mediastinoscopy. After more than sixty years of great service 'the golden age' of cervical mediastinoscopy in mediastinal staging of NSCLC seems to be over.

Another emerging problem is the increasing detection of small intrapulmonary nodules as a result of increasing CT sensitivity, due to acquisition and reconstruction developments. Simultaneously, pulmonary CT for lung cancer detection is increasingly employed. What should we do with such small nodules? What are the rules that determine whether we resect or do follow up for these small nodules? Different lung cancer screening groups as the NELSON study have developed rules [36-38]. Most rules dictate size, nodule volume and nodule doubling time as indicators for resection. Proper histological diagnosis of pulmonary nodules is essential to determine the right therapy. Over the last decades new diagnostic techniques in diagnosis of small pulmonary nodules have become available. Small pulmonary nodules (no larger than 30 mm) are a diagnostic challenge [39]. A standard surgical method for acquiring tissue for histological examination is thoracotomy with tactile identification by the surgeon, which is also the most invasive method. Less invasive methods are percutaneous CT-guided needle biopsy and Video Assisted Thoracic Surgery (VATS) [40,41]. Unfortunately needle biopsy has large sampling errors [42]. Various (pre-)operative localization methods to facilitate VATS wedge-resection have been developed and tested. One of these methods is hookwire localization[43].

In **CHAPTER 4** we evaluate the efficacy and safety of CT-guided Percutaneous Hookwire Localization (CT-PHL) prior to VATS.

Complete surgical resection of pulmonary metastases from a broad range of primary tumors has been recommended as a potentially curative treatment in carefully selected patients for decades [44,45]. However, even then, evidence for successful local surgical treatment of pulmonary metastases is weak [46,47]. Stereotactic ABlative Radiotherapy (SABR) has emerged as a potent non-invasive treatment, capable of eradicating small-volume primary or metastatic tumors in the lungs [45,48-50]. The role of SABR in the management of pulmonary metastases is evolving, but it is often regarded as an option secondary to surgery. Medically operable patients, presenting with resectable oligometastatic disease (OMD) [51] are primarily offered resection [52]. Since 2006, SABR has become available in our institution as an alternative for patients with pulmonary OMD. In this group, SABR was offered as a curative treatment option, since the patients of this group were less suitable candidates for pulmonary metastasectomy (PME). Until now, no randomized study between SABR and surgical resection has been performed. For that reason, we compared PME with SABR in a cohort of patients who were allocated to either treatment, as discussed in **CHAPTER 5**.

In general, it is assumed that PME with clear margins entails the best odds of cure for patients with limited pulmonary metastases (oligometastases) from solid tumors and is recommended for various malignancies. Long-term results are scarce and evidence is weak [53,54]. In **CHAPTER 6** we present longterm results from a consecutive cohort treated with PME or SABR for pulmonary oligometastases from various cancers [55].

Lobectomy with systematic lymph node dissection is the standard procedure for medically operable patients with stage I NSCLC, with a 5-year survival of 50% to 70% [56,57]. However a considerable percentage of patients with resectable early stage NSCLC is medically inoperable because of severe comorbidity. Without any antitumor treatment, the prognosis is poor and most of them will die from tumor progression [58,59]. Since the late 1990s, the development of SABR, enabled treatment of small tumor volumes [60]. Advantages of SABR over surgery in stage I NSCLC are less morbidity, the absence of an invasive procedure and hospital admission.

Surprisingly, no randomized trials comparing clinical outcomes after either procedure are available. For that reason, we compared survival rates and patterns of tumor recurrence in a large consecutive cohort of patients with clinical stage I NSCLC (**CHAPTER 7**).

**CHAPTER 8** is a balanced selection of unique patient cases which represent the borderlands of thoracic neoplasms, both malignant and benign. The cases demonstrate and emphasize why surgery always has to start with a solid strategy. As such, this thesis provides an overview of recent diagnostic and therapeutic strategies in the field of thoracic oncology with emphasis on

pulmonary surgery, radiotherapy and interventional radiology. It represents the perspective of an academic setting with many years of experience, both in patient numbers, as well as in the variety of pathology. Based upon that, future developments of the field are contemplated.

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# Surgical Experience and Patient-Related Restrictions Predict the Success of Cervical Mediastinoscopy in Non-Small Cell Lung Carcinoma Lymph Node Staging

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## Introduction

Lung cancer is the leading cause of cancer death in developed countries and accounts for an estimated 20% of all cancer deaths[1]. Five-year survival can be achieved in 40–50% of patients with early stage non-small cell lung carcinoma (NSCLC)[2]. Accurate staging based on tumour size, regional lymph node involvement and presence of metastasis is essential for treatment of NSCLC patients[3–5]. In the absence of metastases, mediastinal lymph node involvement is the most important prognostic factor and determines therapeutic strategies; i.e. patients with mediastinal nodal disease will in general not benefit from upfront surgery[6, 7].

FluoroDeoxyGlucose - Positron Emission Tomography – Computed Tomography (FDG-PET-CT), Endoscopic UltraSound guided-Fine Needle Aspiration and EndoBronchial UltraSound guided-TransBronchial Needle Aspiration (EUS-FNA/EBUS-TBNA) have become the most important techniques in mediastinal lymph node assessment in recent years[8, 9]. Cervical mediastinoscopy was considered to be the reference standard for mediastinal staging of lung cancer. After its introduction in 1957 mediastinoscopy has evolved considerably[10]. Video-assisted mediastinoscopy (VAM) was first reported in literature in 2002[11] and was introduced at our center in September 2008 and from then on used in each mediastinoscopy case. VAM improved visualization and facilitated teaching tremendously[12]. However, no difference in sensitivity or negative predictive value was found when compared to conventional mediastinoscopy[13]. Nevertheless, the revised ESTS guidelines recommend VAM over conventional mediastinoscopy because of its superior visualization and safety[8].

Mediastinoscopy provides access to the upper paratracheallymph nodes (stations 2R and 2 L), the lower paratracheal lymph nodes (stations 4R and 4 L) and subcarinal lymph nodes (station 7)[8,14,15]. The European Society of Thoracic Surgeons (ESTS) guidelines recommend to acquire at least samples from the lower paratracheal lymph nodes (stations 4R and 4 L) and the subcarinal lymph nodes (station 7)[8]. If present, the upper paratracheal lymph nodes should also be biopsied[8].

A well-executed cervical mediastinoscopy has a sensitivity of 76–85% and a negative predictive value of 82–92%[16] with an overall morbidity of 1.07% and mortality of 0.05%[17]. It is however important to realize that these values are largely dependent on the level of experience of the surgeon and the extensiveness of lymph node sampling[18]. Therefore, in daily practice, the actual adequacy and reliability of cervical mediastinoscopy is expected to be lower.

In this study we evaluated the adequacy of mediastinal lymph node sampling at our center over more than a decade. In addition, we analyzed the influence of: (1)surgeon's experience, (2) the use of VAM and (3) patientrelated restrictions (PRR) on the adequacy of lymph node sampling (based on the ESTS guidelines).

## Patients and Methods

This study was conducted in accordance with the guidelines of the University Medical Center Groningen Institutional Review Board.

### Patients

Between January 2001 and December 2014, 225 patients underwent cervical mediastinoscopy for NSCLC lymph node staging. VAM was introduced at our center in September 2008 and from then on used in each mediastinoscopy case. Patient characteristics are summarized in Table 1. Surgical and histological reports were reviewed. Thirty-day follow-up of survivors was complete and no patient was lost to follow-up.

### Adequacy of Lymph Node Sampling

Based on the ESTS guidelines the minimal requirement for adequate lymph node sampling during cervical mediastinoscopy was defined as histologically proven samples from at least the left and right lower paratracheal lymph nodes (station 4 L and 4R) and the subcarinal lymph nodes (station 7)[8].

### Patient-Related Restrictions (PRR)

PRR were defined as intraoperative conditions or findings, which complicated the adequacy of lymph node sampling. An overview of PRR is shown in Table 2.

| Variable[a] | Value |
|---|---|
| Age, years | 62.4 ± 10.1 |
| Sex | |
| Male | 167 (74) |
| Female | 58 (26) |
| Histology primary lung tumor | |
| Squamous cell carcinoma | 118 (52) |
| Adenocarcinoma | 59 (26) |
| Large cell carcinoma | 45 (20) |
| Adenosquamous carcinoma | 2 (1) |
| NSCLC not otherwise specified | 1 (0) |
| Clinical N-status | |
| N0–1 | 116 (52) |
| N2 | 100 (44) |
| N3 | 9 (4) |
| Clinical Stage[b] | |
| IA | 5 (2) |
| IB | 7 (3) |
| IIA | 12 (5) |
| IIB | 45 (20) |
| IIIA | 109 (48) |
| IIIB | 35 (16) |
| IIIC | 3 (1) |
| IVA | 9 (4) |
| IVB | 0 (0) |
| Purpose of cervical mediastinoscopy | |
| Staging | 138 (61) |
| Staging of tumor with unknown histology | 66 (29) |
| Restaging after chemotherapy | 20 (9) |
| Restaging after earlier mediastinoscopy | 1 (0) |
| Video cervical mediastinoscopy | 187 (83) |
| Level of surgeon's experience | |
| Experienced surgeon | 129 (57) |
| Less experienced surgeon | 96 (43) |

[a]Data are presented as mean ± standard deviation or number (%)
[b]Based on the 8th edition of the TNM classification for lung cancer (International Association for the Study of Lung Cancer)
*NSCLC* non-small cell lung carcinoma

**Table 1** Preoperatieve Patient Data (n = 225)

**Level of Surgical Experience**

The level of surgical experience was based on the number of cervical mediastinoscopies performed by individual surgeons. For surgeons who performed at least 40 mediastinoscopies during the study-period the adequacy of lymph node sampling was > 70%. Therefore experienced surgeons were defined as those who performed at least 40 mediastinoscopies during the study-period. Based on these criteria two out of sixteen surgeons could be considered experienced. Both experienced surgeons in this study were trained as thoracic surgeons.

| Variable[a] | Value |
|---|---|
| Mean number of sampled lymph node stations (per patient) | 3.5 ± 1.2 |
| Mean number of samples taken (per patient) | 11.0 ± 7.3 |
| Adequate lymph node sampling | |
| Based on the ESTS guidelines | 127 (56) |
| Patient-related restrictions | 20 (8.9) |
| Adhesions | 7 (3.1) |
| Bleeding, imparing sight | 4 (1.8) |
| Tumor growth into the mediastinum (inablity to reach all stations) | 2 (0.9) |
| Adequate biopsy of very suspicious node (no further biopsies taken) | 2 (0.9) |
| Patient habitus | 1 (0.4) |
| Extremely limited neck mobility | 1 (0.4) |
| No samples taken on left side due to pre-op hoarseness | 1 (0.4) |
| Struma | 1 (0.4) |
| Anomaly of the innominate vein | 1 (0.4) |
| Intraoperative mortality | 0 (0) |
| Thirty-day mortality | 3 (1.3) |
| Post-operative complications | 7 (3.1) |
| Permanent recurrent laryngeal nerve lesion | 3 (1.3) |
| Bleeding (causing respiratory insufficiency and intubation) | 1 (0.4) |
| Pneumonia | 1 (0.4) |
| Pneumothorax treated with chest tube | 1 (0.4) |
| Atrial fibrillation | 1 (0.4) |

[a]Data are presented as mean ± standard deviation or number (%)
*ESTS* European Society of Thoracic Surgeons

**Table 2** Intraoperatieve and Postoperative Patient Data (n = 225)

**Patient-related restrictions (PRR)**
PRR were defined as intraoperative conditions or findings, which complicated the adequacy of lymph node sampling. An overview of PRR is shown in Table 2.

**Follow-up**
Follow-up was obtained directly from outpatient visits or by telephone interview with the patient and/or the referring physician. Thirty-day follow-up was 100% complete.

**Statistics**
Continuous variables were expressed as mean ± SD. Categorical variables were expressed as percentages. Comparisons between groups were performed using Pearson's $X^2$ test or Fisher's exact test as appropriate for categorical variables and the independent samples t-test or Mann-Whitney U test, as appropriate for continuous variables. Univariate variables with $P < 0.10$ were included in the multivariate analysis. Age and gender were forced in the multivariate model. Multivariate logistic regression analyses by means of a forward stepwise algorithm were performed to identify independent predictors of lymph node sampling adequacy. Odds ratios were reported with 95% confidence intervals (CI). Goodness-of-fit of the final logistic regression models was assessed with the Hosmer-Lemeshow statistic.

All calculations were performed using a commercially available statistical package (IBM SPSS Statistics 22.0; IBM Corporation, Armonk, NY). Statistically significant differences were defined as $P < 0.05$.

## Results

**Lymph node sampling adequacy and its predictors based on the ESTS guidelines.**
The overall adequacy of lymph node sampling was 56%. In patients who underwent cervical mediastinoscopy by an experienced surgeon, adequacy

| Variable | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* value | OR | 95% CI | *P* value |
| Age, years | 1.02 | 0.99–1.05 | 0.141 | – | – | – |
| Female sex | 1.51 | 0.81–2.79 | 0.192 | – | – | – |
| Squamous cell carcinoma histology | 1.14 | 0.96–1.36 | 0.147 | – | – | – |
| Video cervical mediastinoscopy | 0.40 | 0.19–0.87 | 0.021 | – | – | – |
| Experienced surgeon | 1.98 | 1.16–3.39 | 0.013 | 1.96 | 1.13–3.41 | 0.017 |
| No patient related restrictions | 6.00 | 1.94–18.59 | 0.002 | 5.94 | 1.90–18.60 | 0.002 |

**Table 3** Predictors of lymph node sampling adequacy by univariate analysis and multivariate logistic regression.

of lymph node sampling was 64%, versus 47% when operated by a less experienced surgeon (P = 0.013, Table 3). When PRR occurred, adequacy of lymph node sampling was 20%, versus 60% when these restrictions did not occur (P = 0.002, Table 3). The distribution of PRR was not different between patients operated by experienced or less experienced surgeons. PRR did not differ significantly between less experienced and experienced surgeons (PRR 7.8% vs. 10.4%, respectively and P = 0.489). Univariate and multivariate logistic regression analyses of lymph node sampling adequacy are shown in Table 3. Multivariate analysis revealed level of surgeon's experience and PRR as independent predictors of lymph node sampling adequacy. The Hosmer-Lemeshow goodness-of-fit test was non-significant, indicating that this multivariate model is a good fit (X2 = 0.24, df= 1, P = 0.878).

**Thirty-day mortality and post-operative complications**
An overview of thirty-day mortality and post-operative complications is provided in Table 2. Thirty-day mortality was 1.3% (n = 3). All deaths were unrelated to cervical mediastinoscopy. Causes of death included cerebrovascular accident and respiratory insufficiency after partial mandibular resection for a second primary tumour, respiratory insufficiency after thoracotomy and rib resection, and multi-organ failure after early bronchial fistula formation following right-sided pneumonectomy.

## Discussion

This study demonstrates that surgical experience as well as PRR are independent and powerful predictors of the adequacy of cervical mediastinoscopy in NSCLC lymph node staging. When an experienced surgeon performs the mediastinoscopy adequate lymph node sampling is almost 2 times more likely than when a less experienced surgeon performs the mediastinoscopy (OR 1.96) and when PRR are not present adequate lymph node sampling is almost 6 times more likely than when PRR are present (OR 5.94). Other studies have also shown that mediastinoscopy yield depends strongly on operator skills [18,19] and lymph node location[20]. The most frequent PRR in this study included adhesions, bleeding (impairing sight), and tumor growth into the mediastinum (inability to reach all lymph node stations). Although PRR did not differ significantly between less experienced and experienced surgeons, one might assume that a more experienced surgeon might be able to overcome certain PRR more easily than a less experienced surgeon. However, our data do not support this assumption. Both surgical experience and PRR proved to be independent predictors in multivariate analysis.

One of the drawbacks of conventional mediastinoscopy is the uncomfortable position for the surgeon. The surgeon has only a narrow view through the instrument and has to find a way among anatomical entities such as; trachea, esophagus, azygos vein, right pulmonary artery, recurrent nerve and pleural space/lung, and depending on patient anatomy; the carotid and innominate arteries. As such, conventional mediastinoscopy is a complex procedure and teaching can also be difficult because of the risk of 'collateral damage'. These events strongly depend on the experience and teaching skills of the surgeon. VAM, with its superior visualization and teaching possibilities, has made the procedure safer and easier to adopt for surgeons in training[21]. In this study the use of VAM was not an independent predictor of adequacy of lymph node sampling, which supports the general observation that the superior visualization with VAM does not lead to a higher quality of mediastinal lymph node sampling compared to conventional mediastinoscopy[13].

Successful treatment of patients with NSCLC strongly depends on strict and reliable staging. The mediastinal lymph node status determines the sequence of treatment modalities. Until recently, mediastinoscopy was the gold standard for invasive mediastinal lymph node staging in NSCLC. Mediastinoscopy provides access to upper paratracheal lymph nodes (stations 2R and 2 L), lower paratracheal lymph nodes (stations 4R and 4 L) and subcarinal lymph nodes (station 7)[14], and has limitations in assessing the posterior subcarinal, lower mediastinal, and hilar lymph nodes [22]. EBUS-TBNA and EUS-FNA have shown to be at least equivalent to mediastinoscopy in sensitivity and negative predictive value[16]. For that reason, and because of the minimally invasive character of these procedures, they are currently recommended to be first choice for invasive mediastinal lymph node staging in lung cancer[8]. EBUS-TBNA and EUS-FNA are safe procedures with minor complications, reported in less than 1% of cases[23,24]. Especially the combination of EBUS-TBNA and EUS-FNA allows complete access to nearly all lymph nodes of the mediastinum[25,26]. However, pathological assessment of the yield of both procedures is only possible by cytology instead of histology. The samples obtained by needle aspiration are non-diagnostic in a significant number of cases[27] and depend strongly on operator skills[22]. These non-diagnostic cases led to the development of Rapid On-Site Evaluation of the aspirate in order to increase accuracy. This is achieved by monitoring on-site microscopy of repeated lymph node aspirations in different directions of the node until representative samples have been obtained[28]. Limitations of our study include the long time frame and the retrospective design.

Both mediastinoscopy and endosonography are complex technical procedures and depend strongly on operator skills and experience. The complexity of a procedure is inversely related to the adoptability of a procedure[29]. Complexity and adoptability determine the steepness of the learning curve of a procedure

and depends on the quantity of procedures performed by the operator. With the growing experience in endosonography, the quantity of mediastinoscopies performed for mediastinal staging in NSCLC is likely to fall back and with it, the adoptability. In this study, we have shown that surgical experience and PRR are key in adequate lymph node sampling. Therefore, in light of the expected further decline in mediastinoscopy numbers, we recommend to limit this procedure exclusively to the armamentarium of the experienced thoracic surgeon.

## Conclusions

Surgical experience and PRR are powerful and independent predictors of the adequacy of cervical mediastinoscopy in NSCLC lymph node staging. Experience and skills vary with the training of the operator. Therefore, a solid training is required in educational programs and every center has to look at its own diagnostic yield and negative predictive value. VAM with its superior visualization and teaching possibilities, makes the procedure safer and easier to adopt for surgeons in training, but does not independently predict the adequacy of lymph node sampling. Since mediastinal lymph node staging is crucial in patient treatment and outcome, we urge that cervical mediastinoscopy should be performed and taught by experienced thoracic surgeons only.

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# Mediastinoscopy: 'The Rise and Fall of the Gold Standard'

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## Short Communication

Mediastinoscopy was developed as a procedure to obtain tissue for histological diagnosis of upper mediastinal masses. Over the last decades mediastinoscopy has been increasingly used for mediastinal lymph node staging in patients with non-small cell lung cancer (NSCLC).

The history of mediastinoscopy originates from the early fifties of the 20th century. In 1954 Harken [1] was the first to insert a laryngoscope through a supraclavicular incision, thus performing a unilateral mediastinoscopy. Five years later, Carlens reported on hundred cases of a cervical suprasternal approach of the superior mediastinum, thereby defining 'cervical mediastinoscopy' as we know it today [2]. Over time the cervical mediastinoscopy underwent several procedural and technical modifications and became the 'gold standard' in oncologic staging of the mediastinum. Pearson proved that mediastinal lymph node involvement in patients with lung cancer resulted in a dismal prognosis and he therefore suggested that subsequent surgical intervention would not change the outcome [3]. His work triggered the development of an internationally accepted mediastinal lymph node map by Mountain and Dressler [4]. One of the typical features that made conventional cervical mediastinoscopy a complex procedure was the 'tunnel' view through the instrument. Through this tunnel, the surgeon had to find his way amongst vulnerable vital structures such as trachea, esophagus, azygos vein, right pulmonary artery, recurrent nerve, pleural space, and lung and also, depending on the patient's anatomy, the carotid and in nominate arteries. It took a surgeon quite some time to acquire routine skills in this complex environment to perform adequate staging of the mediastinum. For the very same reasons, teaching conventional cervical mediastinoscopy is extremely difficult. Therefore conventional cervical mediastinoscopy is considered a complex procedure and its success strongly depends on the skills of the operator. The development of videoscopic

assisted surgery in the eighties of the 20th century opened new perspectives for minimal invasive closed chest surgery and teaching opportunities. The 'operating field' became visible for all participants of the procedure, or even in the room 'next door'. In the late eighties Lerut developed this concept into what is now called video-assisted mediastinoscopy (VAM) [5]. The uncomfortable 'tunnel-view' of conventional cervical mediastinoscopy transformed into a clear 'operating field' on a flat screen with highly detailed images which allowed better vision on the vital mediastinal structures as well as the abnormal tissue and lymph nodes. Moreover, it proved to be a major improvement for teaching purposes without compromising the procedure itself [6]. Although the above mentioned advantages of VAM are obvious, the sensitivity and negative predictive values of VAM and conventional cervical mediastinoscopy are not different [7]. At present the ESTS guidelines on mediastinal staging recommends performing VAM [8].

Cervical mediastinoscopy has a mortality of less than 0.5% and morbidity of 2.5%. Complications are rare in experienced hands [9]. Cervical mediastinoscopy allows access to lymph node stations 2R, 2L, 4R, 4L, 7, 10R and 10L. The posterior subcarinal nodes, para-esophageal nodes, pulmonary ligament nodes, subaortic nodes, and para-aortic nodes cannot be reached and therefore they cannot be biopsied. As mentioned before, during the last decades the main reason to perform a cervical mediastinoscopy was staging of patients with operable non-small cell lung cancer (NSCLC). In fact, for many decades, cervical mediastinoscopy was the gold standard for staging the mediastinum with a sensitivity between 79% and 93%, specificity of 100% and a negative predictive value of 91% [10,11]. Due to new technologies such as positron emission tomography (PET) and endoscopic ultrasound techniques, the diagnostic algorithm of NSCLC has changed. The number of mediastinoscopies decreased by more than 50% in many institutions [12]. Integrated PET-CT became clinically available in 2000 and it significantly improved diagnostic accuracy and sensitivity of preoperative mediastinal staging in NSCLC compared with that of CT alone or PET alone [13]. Yet PET-CT has still a considerable false positive and negative outcome in NSCLC especially in early stage and central tumors. For this reason, mediastinal abnormalities identified on PET-CT still need pathological confirmation [14]. The endoscopic ultrasound techniques EBUS-TBNA (EndoBronchial UltraSound-guided TransBronchial Needle Aspiration) and EUS- FNA (Endoesophageal UltraSound Fine Needle Aspiration) made a rapid evolution in staging patients with NSCLC. Especially combined EBUS-EUS allows for better evaluation of lymph node stations compared with a single technique alone, since both techniques are complementary. The sensitivity, specificity, negative predictive value, and diagnostic accuracy of combined EBUS-EUS were 91%, 100%, 96% and 97%, respectively [15]. Combined EBUS-EUS covers almost

all the lymph node stations in the mediastinum and also the commonly involved metastatic structures below the diaphragm. The complication rate of endoscopic ultrasound techniques is approximately 0.05% and no mortality has been reported in the literature [16]. These endoscopic ultrasound techniques are also used for the more advanced stage IIIa-N2, in primary staging and for restaging after induction therapy. Clinical trials are underway to answer the question whether cervical mediastinoscopy is still necessary when combining such novel approaches. The ease of EBUS-EUS makes it an ideal staging test: fast, accurate, high negative predictive value, no anesthesia, real-time imaging, safe, and well tolerated. Similar to mediastinoscopy, EBUS-EUS is also a procedure in which its success in staging depends on the skills of the operator [17]. Experience and skills (quality) varies with the training (quantity) of the operator. Therefore, a solid training is required in educational programmes and every center has to look at its own diagnostic yields and negative predictive values of staging procedures. The decreasing numbers of cervical mediastinoscopy will compromise the quality of the procedure and the experience of the operator, as quality comes with quantity. The thoracic surgical community has to be aware of this quality-issue and must find a solution. After more than sixty years of great service 'the golden age' of cervical mediastinoscopy seems to be over. Its role in the investigation of the upper part of the mediastinum and its role in staging of NSCLC have to be redefined.

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# CT-guided percutaneous hookwire localization increases the efficacy and safety of VATS for pulmonary nodules

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**Abbreviations list**
VATS: Video assisted thoracic surgery
CT: Computed tomography
PHL: Percutaneous hookwire localization
CT-PHL: CT-guided percutaneous hookwire localization
GGO: Ground glass opacity

## Introduction

Pulmonary nodules are intraparenchymal densities that are at least moderately well marginated and no larger than 30 mm in its maximum diameter.[1,2] The adjective small has been used to describe nodules that are less than 10 mm in diameter.[2] Recent results from the NELSON study states cancer probabilities in patients with CT-detected pulmonary nodules ranging from 0.4% in nodules <5 mm in diameter to a probability of 15.2% in nodules with a diameter of >10 mm.[3] Follow-up of pulmonary nodules can be performed according to the Fleischner criteria [4,5] or with a combination of volume and volume doubling time of the largest nodule.

A standard surgical method for acquiring tissue for histological examination is thoracotomy with tactile identification by the surgeon.[6] However, thoracotomy is also the most invasive method with an operative mortality of 3-7% for malignant nodules and less than 1% for benign nodules.[7] Less invasive methods are percutaneous CT-guided needle biopsy and VATS.[8,9] Unfortunately percutaneous CT-guided needle biopsy has large sampling errors for both GGO and small pulmonary nodules.[10,11] Various (pre-)operative localization methods to facilitate VATS wedge-resection have been developed

and tested. These localization techniques can be classified into three main groups. The first group consists of intraoperative use of ultrasonography or pressure sensors.[12–14] The second group consists of techniques wherein percutaneous localizers, including hookwires, contrast media, and radiotracers are inserted.[15–17] The third group consists of techniques wherein localizers are inserted transbronchially in which specialized localization equipment and imaging techniques such as CT-fluoroscopy are required.[18] Microcoils, radiolabeling, and hook-wire localization techniques have currently the highest level of evidence for efficacy and safety.[19–24]

The aim of this study was to evaluate the efficacy and safety of CT-PHL prior to VATS in terms of complete resection, histological diagnosis, complications, conversion rate to thoracotomy, and duration of procedures.

## Materials and methods

### Patients

Patients who underwent CT-PHL prior to VATS were prospectively included. Selection criteria were nodule(s) not well approachable with fine needle biopsy, both in size and/or anatomical location. When more pulmonary nodules were present the anatomical best accessible nodule was chosen, identified, and marked with the hookwire. Data were collected from the electronic patient record and the picture archiving and communication system. Data on gender, age, indication,history of malignancy, nodule count, nodule location, nodule diameter, and distance of the nodule to the pleural surface were collected. Informed consent was obtained in all patients.

### CT-guided percutaneous hookwire localization

All imaging was performed by volume scanning with the same multidetector (64 slice) CT scanner (Siemens™, Erlangen, Germany). Two different types of nodule localization systems were used. Initially, Somatex™ Localization Kit S-R (needle diameter 20 gauge), followed by Somatex™ Duo-System localization set (needle diameter 20 gauge, Fig. 1). The latter was employed for the easier usability and the improved double-thorn marking and anchorage system. In both systems the folded hookwire is enclosed within the 20G guidance needle. Optimal puncture site, angle and route were determined from previous CT-scans (Fig. 2). Following local anesthesia of the puncture site, the tip of the needle was positioned in a two-step action as close as possible to the nodule. In the first step the needle containing the folded hookwire was positioned within the boundaries of the chestwall, with the tip just outside the parietal pleura. After verification of the position and angulation, the needle was advanced into the lungparenchyma to reach the nodule and the hookwire was allowed to spread its anchoring hooks

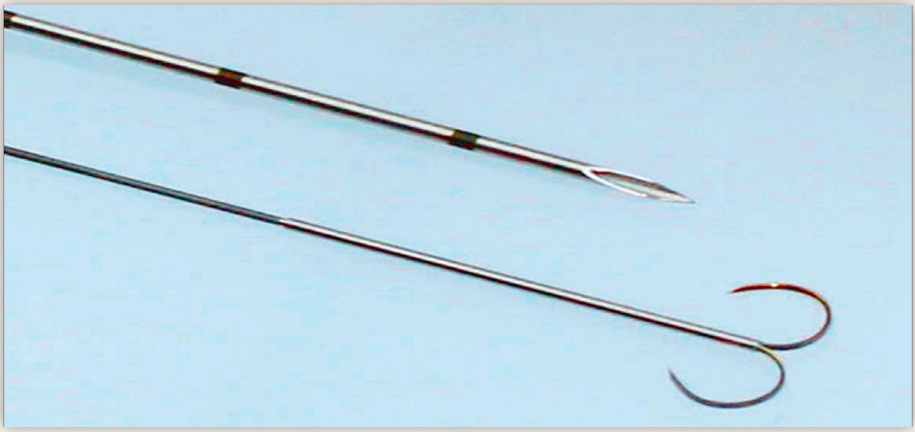

**Figure 1.** Somatex™ duo-system localization set (needle diameter 20 gauge).

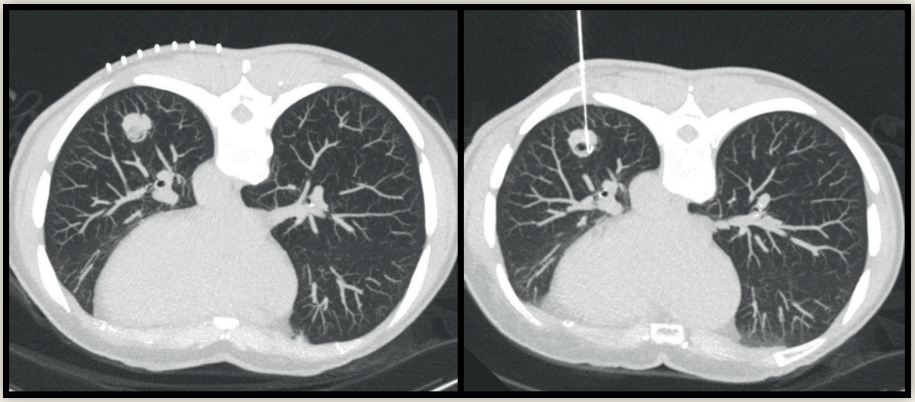

**Figure 2.** (left) Different stages of CT-guided percutaneous hookwire localization. For demonstration purposes an example of one of the largest nodules was chosen. Optimal puncture site is chosen. **Figure 3.** (right) Different stages of CT-guided percutaneous hookwire localization. For demonstration purposes an example of one of the largest nodules was chosen. The hookwire system is inserted into the nodule.

by withdrawing the guidance needle(Fig. 3). With a final control CT-scan the position of the hookwire relative to the nodule was established and simultaneously the chest was checked for complications (eg, pneumothorax, parenchymal haemorrhage). Next, MIP (Maximum Intensity Projection), 2D and 3D-reconstructions were made available for the surgeon to be viewed dynamically during subsequent VATS (Fig. 4). Complications during the hookwire localization were divided in major and minor complications depending on the necessity of an intervention. Procedure time of the CT-PHL procedure was defined as time from first scan to the time of last control scans.

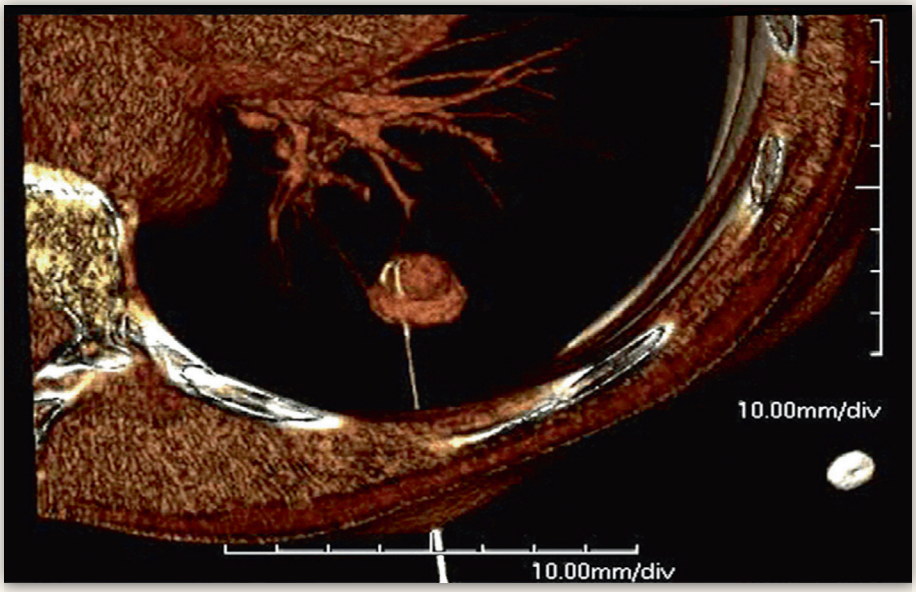


**Figure 4.** Different stages of CT-guided percutaneous hookwire localization.
For demonstration purposes of one of the largest nodules was chosen. 3D reconstruction.

**Video assisted thoracic surgery**

Wedge resection of the localized area was performed according to standard surgical procedures. The resected wedge with hookwire was retrieved with an endobag via one of the port incisions. Palpation of the wedge confirmed the resection of the pulmonary nodule. The duration of the VATS was defined as the time from first incision to the time the incisions were closed.

**Pathology**

Macroscopic and microscopic postoperative pathological examination was reported in the patients record and discussed at the multidisciplinary oncology meeting. Information on diagnosis and completeness of the resection was obtained.

**Statistics**

Patient characteristics were reported as median and ranges or percentages The chi-squared or Fisher's exact test was used to test differences. P-values less than 0.05 were considered statistically significant. Data gathering and all statistical analysis were performed with IBM SPSS software (version 22).

## Results

**Patient characteristics:**
Between April 2006 and June 2015, 150 CT-PHL with subsequent VATS were performed in 147 patients in the same academic hospital. Over time, three

| | | No. of patients | Percentage |
|---|---|---|---|
| Gender | Male | 87 | 58.0% |
| | Female | 63 | 42.0% |
| Age on day of procedure | < 45 years | 14 | 9.3% |
| | 45 - 65 years | 85 | 56.7% |
| | > 65 years | 51 | 34.0% |
| Cancer history | Yes | 130 | 88.4% |
| | No | 17 | 11.6% |
| Amount of nodules | 1 | 68 | 45.3% |
| | 2 – 4 | 32 | 21.3% |
| | Multiple | 48 | 32.0% |
| | Ground glass opacity | 2 | 1.3% |
| Location marked nodule | Upper lobe left lung | 30 | 20.0% |
| | Lower lobe left lung | 47 | 31.3% |
| | Upper lobe right lung | 27 | 18.0% |
| | Middle lobe right lung | 13 | 8.7% |
| | Lower lobe right lung | 33 | 22.0% |
| Nodule diameter on CT | 0 - 5 mm | 23 | 15.3% |
| | 6 - 10 mm | 77 | 51.3% |
| | 11 - 15 mm | 31 | 20.7% |
| | 16 - 20 mm | 15 | 10.0% |
| | 21 - 25 mm | 2 | 1.3% |
| | Ground glass opacity | 2 | 1.3% |
| Nodule distance to pleural surface | 0 - 5 mm | 64 | 42.7% |
| | 6 - 10 mm | 40 | 26.7% |
| | 11 - 15 mm | 20 | 13.3% |
| | 16 - 20 mm | 11 | 7.3% |
| | 21 - 25 mm | 11 | 7.3% |
| | 26 - 30 mm | 4 | 2.7% |
| Diagnosis | NSCLC | 32 | 21.3% |
| | Metastasis | 84 | 56.0% |
| | Benign | 34 | 22.7% |

NSCLC, non small cell lung carcinoma

**Table 1** Characteristics of patients, nodule, and procedure (n = 150)

patients had a second procedure for diagnosis of a new small pulmonary nodule (metachronous lesion). The patient group consisted of 86 males and 61 females, with a median age of 61 years(range 10-85 years). Hundred-thirty of 147 patients (88.4%) had a history of cancer or underwent a previous oncologic treatment (Table 1)

**Nodule characteristics:**
All nodules had diameters <25 mm (median 9, range 4-24) with a median distance to the pleural surface of 7 mm (range 0-29). Sixty-eight (45.3%) patients had one single nodule, 18 (12.0%) patients had two nodules, 10 (6.7%) three nodules, 4 (2.7%) four nodules, and 48(32.0%) had multiple nodules. Two GGO lesions were detected (1.3%)(Table 1).

**CT-guided percutaneous hookwire localization:**
All nodules were localized and marked successfully during the CT-PHL. In the vast majority (94%) of patients a single hookwire was required, in eight patients a second or third hookwire was used to mark another nodule during the same procedure. Suboptimal hookwire localization occurred in only one patient as was observed at control CT, therefore an additional hookwire was successfully inserted (Table 2). The median duration of the procedure was 26 min (range 5-72). The procedure time and complication rate were not significantly influenced by nodule diameter (P = 0.22, respectively, P = 0.51) or distance of the nodule to the pleural surface (P = 0.34, respectively,P = 0.43). Hookwire dislodgement did not occur in any of the 150 CT-PHL

| | | Count | Percentage |
|---|---|---|---|
| Hookwire type | Somatex Duo System | 127 | 84.7% |
| | Somatax Localisation Kit S.-R. | 23 | 15.4% |
| Amount of wires | 1 | 142 | 94.7% |
| | 2 – 3 | 8 | 5.3% |

**Table 2** Hookwire procedure characteristics

procedures. Complications of CT-PHL were found in 34% of patients. Minor complications occurred in 40 patients (26.7%), major complications requiring intervention in 11 patients (7.3%) (Table 3). Nine patients developed a pneumothorax requiring tube drainage awaiting VATS. Two patients developed a haematothorax after the VATS. At re-operation bleeding of an intercostal artery at the puncture site was diagnosed.

**Video assisted thoracic surgery:**
All 150 patients underwent the planned wedge resection. All nodules but one were resected successfully at the first attempt (99.3%). In one patient there was no palpable nodule in the resected wedge, which was confirmed with

| | | Count | Percentage |
|---|---|---|---|
| Hookwire complications | Pneumothorax, no intervention needed | 35 | 23.3% |
| | Pneumothorax, intervention needed | 9 | 6.0% |
| | Parenchymal haemorrhage, no intervention needed | 2 | 1.3% |
| | Intercostal artery puncture | | |
| | - Diagnosed at re-operation for hematothorax | 2 | 1.3% |
| | - Diagnosed after control CT-scan, no intervention | 1 | 0.7% |
| | Adverse reaction on lidocaïne | 1 | 0,7% |
| VATS complications | Persisting air leakage > 3 days | 6 | 4.0% |
| | Transfusion for hematothorax | 1 | 0.7% |
| | Hematothorax requiring intubation and re-operation | 1 | 0.7% |
| | Pneumonia, respiratory insufficiency requiring intubation | 1 | 0.7% |
| Mortality | Death <30 days | 2 | 1.3% |
| | In hospital mortality | 1 | 0.7% |
| Wedge resection | Successful | 143 | 95.3% |
| | Conversion to (mini-) thoracotomy due to: | | |
| | - Central position PN | 2 | 1.3% |
| | - Insufficient single lung ventilation | 2 | 1.3% |
| | - Bleeding | 1 | 0.7% |
| | - Wire dislodgement | 1 | 0.7% |
| | - Stapler dysfunction | 1 | 0.7% |
| Radical resection of malignancy (n = 116) | Yes | 110 | 96.0% |
| | No, received further treatment | 6 | 4.0% |

VATS, video-assisted thoracoscopic surgery.

**Table 3** Procedure characteristics

frozen section. The VATS was converted to mini-thoracotomy and the nodule was found 10 mm above the resection site. Most likely this was caused by wire dislodgement between placement of the hookwire and wedge resection during VATS. Hookwire dislodgement could have happened during transport to the OR, during positioning of the patient on the operating table, during initiation of single lung ventilation, and collapse of the non-ventilated lung, or due to manipulation during the VATS procedure.

The median duration of the VATS procedure was 49 min (range 14-169). Conversion to (mini-) thoracotomy was necessary in seven patients(4.7%) (Table 3). Postoperative complications of VATS occurred in nine patients (6%). Six minor complications and three major complications occurred (Table 3).

The hospitalization time ranged from 2 to 52 days (median 4.5 days). The overall mortality was 2% (three patients). Two patients died within 30 days of surgery. In one patient NSCLC was diagnosed after CT-PHL and VATS wedge resection during screening for lung transplantation. The patient refused any further treatment. In the second patient CLL was diagnosed and developed a severe pneumonia in the postoperative course and died. The third patient died in hospital after 52 days due to complications following lobectomy and was not directly related to the CT-PHL and VATS wedge resection.

**Diagnosis**

In five patients (3.3%) no palpable nodule or macroscopic abnormality was found in the wedge resection during VATS despite the radiological abnormalities. Nevertheless microscopic pathologic examination revealed malignancy stressing the importance of CT-PHL for GGO and VATS wedge resection.

Pathologic examination revealed in total 32 primary lung cancers, 84 metastases, and 34 definite non-neoplastic pathologies. Radical resection was achieved in 110 of the 116 malignancies (94.8%). Pathology diagnosis, metastasis frequency, and radical resection are displayed in Tables 1 and 3

## Discussion

Commonly used non-invasive imaging evaluation for pulmonary nodules are CT and positron emission tomography/computed tomography with radiolabeled [18F]-2-fluro-deoxy-D-glucose with diagnostic accuracies of 85% and 93% for malignancy.[6,25] A shortcoming of these imaging techniques is their variability in diagnostic sensitivity with different lesion size, especially with GGO and small nodules. [25,26] With the advent of VATS, thoracotomy is no longer required for pulmonary nodule removal. However palpation, manual or by instrumentation, of GGO and nodules is difficult or even impossible during

VATS.[27] In VATS, nodules less than 10 mm in diameter and located more than 5 mm deep from the pleural surface may be associated with a 63% chance of failure to be identified.[28] Furthermore, the operative procedure time may be prolonged by spending time on finding the small pulmonary nodule and the minimally invasive procedure is in more than 50% converted to (mini-) thoracotomy.[28] The advantages of VATS, less traumatic access to the thoracic cavity, less postoperative pain, a lower complication rate, less restriction in post-operative pulmonary function test, and earlier return to preoperative activity, is offset by conversion to (mini-)thoracotomy.[29,30]

In theory, the combination of a localization technique and VATS makes the procedure more efficient by means of radical resection, diagnostic accuracy, reduction of procedure time, and a lower conversion rate to (mini-)thoracotomy.[19] The highest level of evidence for efficacy and safety currently appears to support microcoils, radiolabeling, and hookwire localizationtechniques.[19–24] A randomized controlled trial comparing CT-PHL to 99n Technetium labeled albumin localization in small nodules did not show significant difference between both techniques. However, both techniques were significantly better at localizing nodules than finger palpation during VATS.[20] CT-PHL with mammography localization needles is first mentioned in the early nineties.[31] Since then various localization techniques have been developed and tested, ranging from straight hook needles to self-modified hookwires.[27,32] Gradually the straight hookwire evolved into a double-thorn localization system that is still used in both mammographic and pulmonary localization. Both types of hookwires successfully localized nodules. The median time of the CT-PHL was less than half an hour, similar as in other studies.[27,33– 35] Various authors stated that pre-operative CT-guided localization made VATS resection more efficient in time.[34] Ciriaco et al mentioned VATS times of 40 ± 7 min with nodule localization versus 75 ± 12 min without CT-PHL.[35,36] In that study, nodule localization enabled VATS resection in 31/ 58 patients, which would not have been feasible otherwise since these nodules were not visible or palpable.[36] Our study confirms that observation. The conversion rate of VATS to thoracotomy for nodules without hookwire localization ranges up to 54%.[28] We found in our study a conversion rate of 4.7%, which is within the range (0-10.3%) mentioned in other studies.[32,33–35,37,38]

The most common complication of CT-PHL in our series was pneumothorax in 29.3% (44/150). The pneumothorax rate in our study is within the range of 12.8-68% reported by others.[27,33,34,37] Localized parenchymal hemorrhage occurred in 2% after CT-PHL. All of them where only noted as a slightly increased GGO around the needle pathway on direct CT scanning after placement and did not require intervention . The parenchymal haemorrhage rate was well below the range of 8.9-40.8% reported in the literature.[27,33,35]

Only one (0.7%) hookwire dislodgement occurred. If hookwires dislodge, this happens during transportation of the patient, during deflation of the lung, or during resection. The dislodgement rate in our study is within the 0-7.6% range reported in the literature.[27,33,37,38] In our study, we successfully localized nodules with a diameter between 4 and 24 mm and with a distance to the pleural surface of 0-29 mm. No significant correlation was found between nodule size and the procedure times of the CT-PHL and VATS. Neither did we find a significant correlation between complications of CT-PHL and VATS.

In three procedures, we found a discrepancy between CT-PHL findings and peri-operative findings. Three nodules were difficult reachable during VATS due to central location (n = 2, Table 3) or anatomical position causing bleeding (n = 1, Table 3). Wedge resection after conversion to thoracotomy was therefore, necessary. In advance, CT-PHL should be discouraged for centrally located lesions or lesions in difficult anatomical position. Instead, immediate sublobar resection example segmentectomy, open, or by VATS, should be offered to these patients.

## Conclusion

This study confirms the results of previous studies in which CT-PHL increases the identification rate of pulmonary nodules, reduces VATS time, and decreases conversion to thoracotomy.

Moreover, our study also demonstrates that the combination of CT-PHL and VATS wedge resection has a very high diagnostic accuracy and therapeutic efficacy. For that reason we advocate the combination of CT-PHL and VATS wedge resection as the method of choice to get diagnosis of superficial pulmonary nodules.

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# Pulmonary oligometastases: Metastasectomy or stereotactic ablative radiotherapy?

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## Introduction

Complete surgical resection of pulmonary metastases from a broad range of primary tumours has been recommended as a potentially curative treatment in carefully selected patients for decades[1,2]. Five year survival rates in the range between 30% and 65% have been reported[1,3]. However, evidence for local surgical treatment of pulmonary metastases is weak; there are no results from prospective randomised controlled trials evaluating the role of pulmonary metastasectomy (PME) in the management of these patients[4–6].

Stereotactic ablative radiotherapy (SABR) has recently emerged as a potent non-invasive treatment capable of eradicating small-volume primary or metastatic tumours in the lungs[2,7–9]. The role of SABR in the management of pulmonary metastases is evolving, but it is often regarded as an option secondary to surgery, both due to a longer experience with surgical resection and the conceptually straightforward approach of radical resection of a lesion followed by microscopic and genomic examination of the specimen. Hence, medically operable patients presenting with resectable oligometastatic disease (OMD)[10,11] are typically offered resection as a primary option[12], which is in accordance with a number of national and international guidelines (www.onc oline.nl; www.nccn.org/professionals/physician_gls/f_guidelines.asp#site; www.esmo.org/education-research/esmo-clinical-practice-guidelines.html). In 2006, SABR was established at our institution and became available as an alternative for patients with pulmonary OMD who were to be offered a curative treatment option, but were considered to be less suitable candidates for PME due to performance status – often in the elderly – or to comorbidity, or recent major surgery such as, e.g., large bowel surgery plus hemihepatectomy. Presently, no studies comparing PME with SABR for OMD have been reported, not even retrospective analyses. This is the first study comparing PME with SABR in a cohort of patients who were allocated to either treatment via a university hospital-based multidisciplinary team (MDT).

The primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS), freedom from local progression at the treated metastatic site (FFLP), and freedom from failure of a local-only treatment strategy (FFLS) after PME or SABR[13]. We expected improved survival after PME compared with SABR due to patient selection penalising SABR and analysed factors potentially influencing the outcome.

## Materials and methods

### Patient selection

The study cohort consisted of a consecutive series of patients with up to five pulmonary metastases from a solid tumour in whom PME and SABR were considered potentially curative, as concluded at the thoracic oncology MDT. This team consisted of thoracic oncology pulmonologists, cardiothoracic surgeons, radiation oncologists, radiologists, nuclear physicians, and pathologists. Pulmonary lesions exhibited progression on serial thoracic CT and/or FDG-uptake on whole-body 18-F-FDG PET. The primary tumour and any extrapulmonary metastases had to be curatively resected or thermo-ablated previously so that the pulmonary lesions were the only manifestation of disease at the time of PME or SABR. Pathological confirmation of pulmonary lesions prior to treatment was not required, but all patients undergoing PME were found to harbour metastases in the resected specimens. Curative intent was defined as either resection or ablation of all metastases visible on thoracic CT. The study was submitted to the institutional review board of our university and was declared exempt from ethical approval.

### Follow-up

Patients were followed with regular CT of thorax and abdomen every 3 months for 2 years, and every six months thereafter. Tumour assessment was according to RECIST 1.1 criteria. In case of disease progression, further treatment options were again discussed at the multidisciplinary boards. Further local treatment for metastases – in the sense of a local-only treatment strategy, i.e., without administration of peri-interventional systemic treatment – was advised if less than five new lesions were present and as long as all new lesions were again amenable to resection (pulmonary or elsewhere), SABR, or radiofrequency ablation in case of liver metastases.

### Treatment

Surgery was performed by cardiothoracic surgeons via thoracotomy or video-assisted thoracic surgery (VATS). SABR was performed at a dedicated stereotactic unit (Novalis, Brainlab, Feldkirchen, Germany) according to our

institutional treatment protocol. A total dose of 60 Gy was administered. The number of fractions was adapted to risk of toxicity: three fractions of 20 Gy were given, if all lesions were surrounded by lung tissue and were lying outside of a two-centimetre volume surrounding the proximal airways as defined in RTOG protocols[7]; five fractions of 12 Gy were given for lesions adjacent to the thoracic wall; eight fractions of 7.5 Gy were administered, if the whole or part of a lesion was found within the two-centimetre volume surrounding the central proximal airways. Treatment planning was based on a 4D-CT accounting for respiratory movements, patient positioning was verified and corrected online at each fraction using the ExacTrac system (Brainlab, Feldkirchen, Germany).

**Statistical analysis**

A retrospective analysis with updated follow-up was performed in February 2013. Overall survival measured from PME or start of SABR was the primary endpoint. The following secondary endpoints were also estimated: PFS with progressive disease based on RECIST 1.1 criteria or death as event; freedom from local progression (FFLP) with progression/recurrence at the treated site as event. In this study, a growing mass without air bronchogram on CT at the treated site, or regrowth of a mass that had already completely or partially disappeared, was rated local progression after SABR. After surgery, development of a new mass attached to the resection-clips was considered to be local recurrence. Patients remained at risk for local progression as long as they were still eligible for further local treatment of metastases eventually arising at new or previously treated locations (local progression) and were censored at the date of systemic progression not involving the previously treated site, if the multidisciplinary tumour board decided against further local treatment of the new metastases. The event for freedom from failure of local-only strategy (FFLS), adopted and modified from[13], was the date at which there were no more local treatment options as decided by the MDT.

Survival times were estimated applying the Kaplan–Meier method and curves were compared using the log-rank test. Further analysis was limited to the following factors due to the relatively small sample size (n=110) and limited number of events (n = 52): age; gender; primary tumour (colorectal versus other); metastasis-free interval (MFI), defined as the interval from diagnosis of the primary tumour to occurrence of the very first metastasis (irrespective of its location, lung or other; and irrespective of eventual prior treatment, e.g., of liver metastases by radiofrequency ablation or resection); number of lesions; size of largest lesion; previous chemotherapy. STATA version 11.0 (College Station, TX, USA) was used for analyses.

## Results

Consecutive patients treated between 1st January, 2007 and 31st December, 2010 were included in the study. Patient and tumour characteristics are displayed in Table 1. The multidisciplinary panel regarded PME as treatment of first choice and advised SABR for patients considered to be less suitable candidates for surgery, and the treatment proposal (PME or SABR) was

| | PME ($n$ = 68) | SABR ($n$ = 42) | Total ($n$ = 110) | $p$-Value |
|---|---|---|---|---|
| Male/female | 37/31 | 27/15 | 64/46 | 0.308 |
| Age (median, range) | 61 (18–81) | 70 (49–89) | 63 (18–89) | *<0.001* |
| Primary tumour | | | | *<0.001* |
| Colorectal | 39 (57%) | 31 (74%) | 70 (64%) | |
| Sarcoma | 18 (27%) | 1 (2%) | 19 (17%) | |
| Non-small-cell lung cancer | 0 | 6 (14%) | 6 (5%) | |
| Renal | 5 (7%) | 1 (2%) | 6 (5%) | |
| Other | 6 (9%) | 3 (7%) | 9 (8%) | |
| Metastasis free interval, months (median, range) | 18.0 (0–138) | 12.7 (0–86) | 15.7 (0–138) | *0.045* |
| Number of lesions | | | | 0.821 |
| 1 | 40 (59%) | 27 (64%) | 67 (61%) | |
| 2 | 21 (31%) | 7 (17%) | 28 (25%) | |
| 3–5 | 7 (10%) | 8 (19%) | 15 (14%) | |
| Size of largest lesion, centimetre (mean, 95% CI) | 2.0 (1.7–2.4) | 1.7 (1.4–2) | 1.9 (1.7–2.1) | 0.162 |
| Prior chemotherapy for metastatic disease | 8 (12%) | 13 (31%) | 21 (19%) | *0.013* |

PME, pulmonary metastasectomy; SABR, stereotactic ablative radiotherapy for pulmonary metastases.

**Table 1.** Patient-, tumour and pretreatment characteristics.

effectuated in all cases. Patients receiving SABR were older, had more colorectal and non-small-cell lung cancers, but less sarcomas, and had a shorter metastasis-free interval, while number and size of treated lesions were not different in the two groups (Table 1). The majority of patients receiving PME (n = 68) underwent wedge resections (n = 52; 76%), fourteen of which were performed by VATS, and thirty-eight with an open procedure. Nearly one quarter of the surgical patients (n =15) underwent lobectomy, one had a left pneumonectomy for five colorectal metastases in the left lung. Resection margins were reported as microscopically free in 62 (91%) of the cases and not free from tumour in six. The majority of patients receiving SABR (n = 42) were treated with three fractions (n = 23; 55%), nine and ten patients received five and eight fractions, respectively.

With minimum follow-up of 25 months (median 43; interquartile range 36–60), there were no significant differences in OS between SABR and PME (logrank-test, p = 0.43; HR 0.79, 95% CI 0.43–1.42; p = 0.427). Three years after SABR or PME, estimated OS was 60% and 62%, respectively (Table 2). None of the factors tested at univariable analysis were significant, therefore

multivariable analysis was forgone (Appendix Table 1A). In particular, the administration of prior chemotherapy (HR 1.04 CI 0.4–2.09; p = 0.895), age (HR 1.00 CI 0.98–1.03; p = 0.865), and metastasis-free interval (HR 0.99 CI 0.98–1.01; p = 0.187) were not significant with hazard ratios closely around one. Fig. 1 shows the Kaplan– Meier OS graph comparing PME and SABR.

Patterns of progression and post-treatment management did not differ between SABR and PME (Table 3). There were 4 (10%) and 7 (10%) local recurrences/progressions at the treated site after SABR and PME,

| Percentages and 95% CI | | 1 year | 2 years | 3 years | 4 years | 5 years |
|---|---|---|---|---|---|---|
| Overall survival | PME | 87 (76–93) | 74 (61–82) | 62 (49–73) | 47 (33–59) | 41 (27–54) |
| | SABR | 98 (84–100) | 86 (71–93) | 60 (42–73) | 60 (42–73) | 49 (25–69) |
| | All patients | 91 (84–95) | 78 (69–85) | 62 (51–70) | 50 (39–60) | 43 (31–54) |
| Freedom from failure of local strategy | PME | 69 (56–78) | 53 (40–64) | 45 (32–57) | 39 (25–52) | n.a. |
| | SABR | 75 (59–86) | 51 (34–66) | 39 (22–56) | 31 (14–51) | n.a. |
| | All patients | 71 (62–79) | 53 (42–62) | 43 (33–53) | 36 (25–47) | n.a. |
| Progression-free survival | PME | 54 (42–65) | 33 (22–45) | 22 (12–33) | 18 (9–30) | n.a. |
| | SABR | 50 (34–64) | 21 (9–35) | 8 (2–22) | 8 (2–22) | n.a. |
| | All patients | 53 (43–62) | 29 (20–38) | 17 (10–26) | 15 (8–24) | n.a. |
| Freedom from local progression | PME | 93 (83–97) | 90 (78–96) | 83 (65–92) | 83 (65–92) | n.a. |
| | SABR | 94 (79–99) | 94 (79–99) | 85 (55–96) | 85 (55–96) | n.a. |
| | All patients | 94 (86–97) | 92 (83–96) | 84 (70–91) | 84 (70–91) | n.a. |

PME, pulmonary metastasectomy; SABR, stereotactic ablative radiotherapy for pulmonary metastases.

**Table 2.** Life-tables for overall survival, progression-free survival, and freedom from local progression.

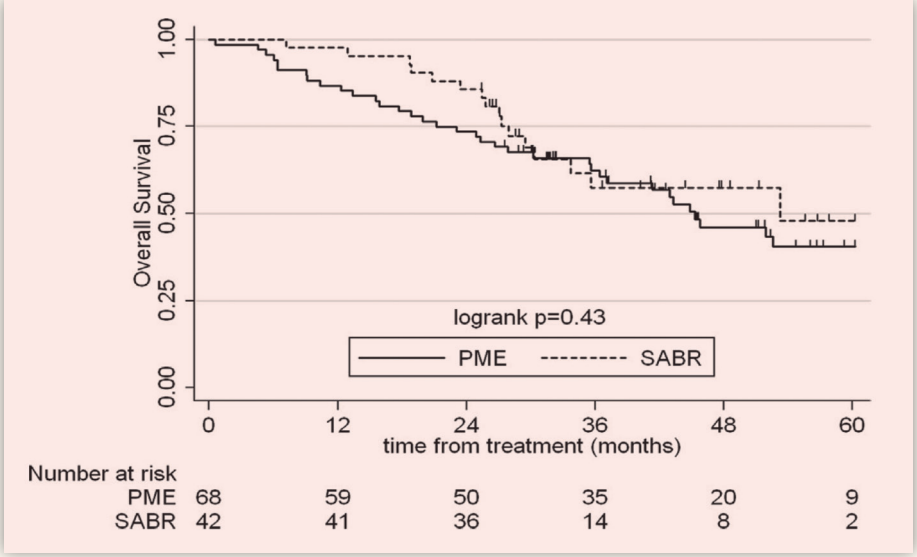


**Fig. 1.** Overall survival.

| | PME ($n$ = 68) | SABR ($n$ = 42) | Total ($n$ = 110) |
|---|---|---|---|
| Died | 35 (51%) | 17 (40%) | 52 (47%) |
| Any disease progression | 51 (75%) | 32 (76%) | 83 (75%) |
| Local progression at treated site | 7 (10%) | 4 (10%) | 11 (10%) |
| Location of first progression | | | |
| Lung only | 25 (49%) | 20 (63%) | 45 (54%) |
| Lung and other organs | 5 (10%) | 3 (9%) | 8 (10%) |
| Other organs only | 21 (41%) | 9 (28%) | 30 (36%) |
| Treatment for first progression | | | |
| Local treatment | 25 (49%) | 16 (50%) | 41 (49%) |
| Chemotherapy | 10 (20%) | 11 (34%) | 21 (25%) |
| Supportive care | 16 (31%) | 5 (16%) | 21 (25%) |

PME, pulmonary metastasectomy; SABR, stereotactic ablative radiotherapy for pulmonary metastases.

**Table 3.** Pattern and treatment of progression after index treatment.

respectively, only one arose after microscopically incomplete resection. The one- and three-year actuarial rates of freedom from local progression at the treated site(s) were 94% and 85% after SABR, and 93% and 83% after PME, respectively (Table 2). PFS at one and 3 years was 50% and 8% after SABR, and 54% and 22% after PME, respectively (logrank-test, p = 0.3) (Table 2; Appendix Fig. 1A), indicating that the predominant patterns of progression were new metastases, the majority of which in turn arose in the lungs (Table 3). Half of the patients suffering progression were offered further local-only treatment of new metastatic lesions at first relapse. This translated into 39% and 45% of the patients remaining free from failure of a local-only treatment strategy at 3 years after PME or SABR, respectively (Table 2; Appendix Fig. 2A). It is important to mention that as long as patients were still candidates for local treatment, they did not receive systemic therapies.

## Discussion

The results of the present analysis are challenging, since they do not support the expectation. Survival was not better after PME – the survival curve after SABR even lying higher at times than the curve after PME – despite assigning PME as treatment of first choice (62% of the cases) and SABR as the second best alternative (38%) via university-hospital-based MDT treatment allocation. The MDT recommended PME unless arguments were provided suggesting that the patient would benefit from non-surgical therapy. Of note, the advice from the multidisciplinary panel was always followed. As expected, this resulted in an unbalanced distribution of a number of factors that would

prima facie suggest a favourable prognosis for patients undergoing PME (Table 1): surgical patients were younger and had a longer metastasis-free interval; most metastases from sarcomas (better prognosis) were resected, while all patients with metastases from non-small-cell lung cancer (worse prognosis) received SABR. No patient had received induction chemotherapy prior to planned local treatment of metastases, but more patients allocated to SABR had received some chemotherapy between primary tumour and presentation at the MDT. However, having received previous chemotherapy yielded a hazard ratio of 1.04 (p = 0.895) at univariable analysis for overall survival making it unlikely that this was a significant factor for unexpected favourable survival after SABR. Postoperative mortality can also not be regarded as explanatory, because only one patient (age 78, metastasis from a sarcoma) died within 30 days after surgery – on the 17th postoperative day – at home from a cardiovascular event. All but one – deceased 2 years post SABR – of the other 51 patients who have died had suffered systemic disease progression prior to death.

A most likely explanation for our results may be a comparably high local tumour control for both modalities. Assessed as freedom from relapse at the treated metastatic site as long as further local treatment (for any other lesions) remained an option, local control at 2 years was comparable at 94% (95% CI 79–99) for SABR and 90% (95% CI 78–96) for PME. For SABR, this local control rate is in the upper range of published results[14]. Removal of metastases by resection is both intuitively appealing and has been shown to be locally effective, but demonstration of its merit in terms of a survival benefit compared with other local or systemic treatments is still lacking[1,3,6]. Non-invasive ablation of metastases using SABR has become possible due to recent technological advances in radiation oncology and therefore has a shorter track record, although high local control of targeted lesions is a well-described phenomenon in a number of clinical settings[2,14–18]. However, when administered in the treatment of non-small cell lung cancer at stage I, it is typically reserved for patients who are medically inoperable and more frail than surgical candidates, which results in OS rates that should not be compared with survival rates after lobectomy[19].

This study has a number of shortcomings. Firstly, it is a retrospective investigation retrieved from a real-life university hospital clinical environment, where only overall survival constitutes a robust endpoint. At last, overall survival will also be the most relevant endpoint in the oligometastatic setting, because no other reason but prolongation of symptom-free survival forms the indication for treating asymptomatic metastases. All other endpoints, including PFS, FFLP, and FFLS, are less robust and carry inextricable traces of clinical judgment. In addition, difficulties in distinguishing local recurrence after SABR from radiogenic local changes are well recognised especially in the NSCLC setting[20,21]. At what point in

time failure of a local-only treatment strategy is concluded is doubtlessly influenced by a number of factors, because it presupposes interpretation of a complex clinical situation and recommending purportedly optimal care for individual patients in the absence of sufficient evidence[5]. It seems interesting, however, that the time-course of this conclusion was quite comparable for both PME and SABR (Table 2), suggesting a window for a considerable percentage of patients who could receive further local treatment for metastases, with a still curative chance. Toxicity of both treatments was generally very mild, had not been scored prospectively and was thus not available for meaningful description. The statistical power to detect any differences between groups and the analysis of subgroups was limited due to the sample size.

The crucial question, in which situations (which kind of) local treatment for OMD confers a relevant clinical benefit, clearly requires comparative prospective clinical research[6] and cannot be answered given the evidence available, including this study. It might also be considered appropriate to investigate local treatment of OMD with the intention to postpone systemic treatment and its toxicities. How this eventually translates into gains in quality-of life, improved survival, and cost effectiveness again requires prospective comparative studies.

In conclusion, in a consecutive cohort of patients with pulmonary oligometastases from a range of solid tumours, pulmonary metastasectomy applied as treatment of first choice did not yield significantly better overall survival compared with the second choice-treatment, stereotactic radiotherapy. The selection bias penalising radiotherapy was thus not reflected in survival outcome. Despite complexity of the subject, which is mainly due to ill-defined patient selection criteria resulting from a broad range of tumour biology and patterns of clinical presentation, prospective comparative studies are clearly needed to further explore both the role and optimal timing of the concept of local therapy – using stereotactic ablative radiotherapy or pulmonary metastasectomy – in oligometastatic disease.

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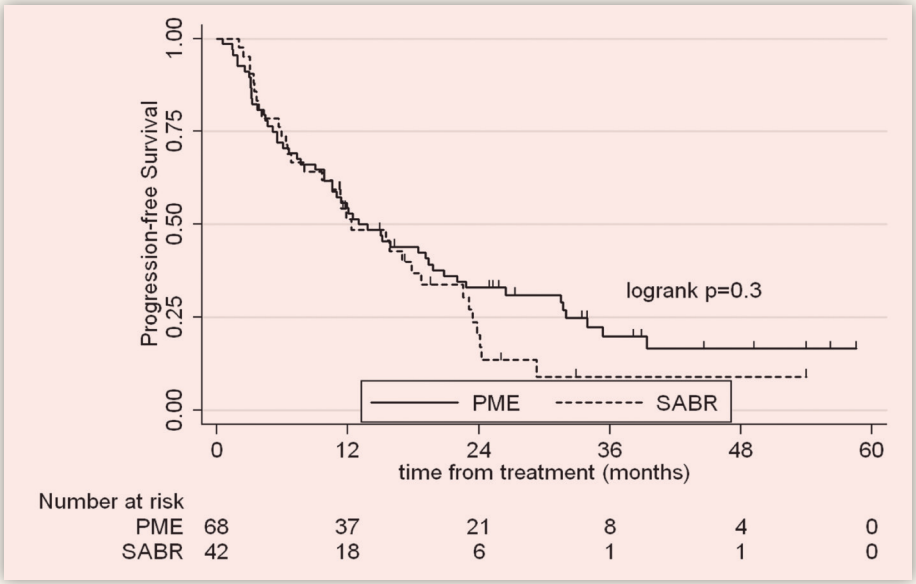
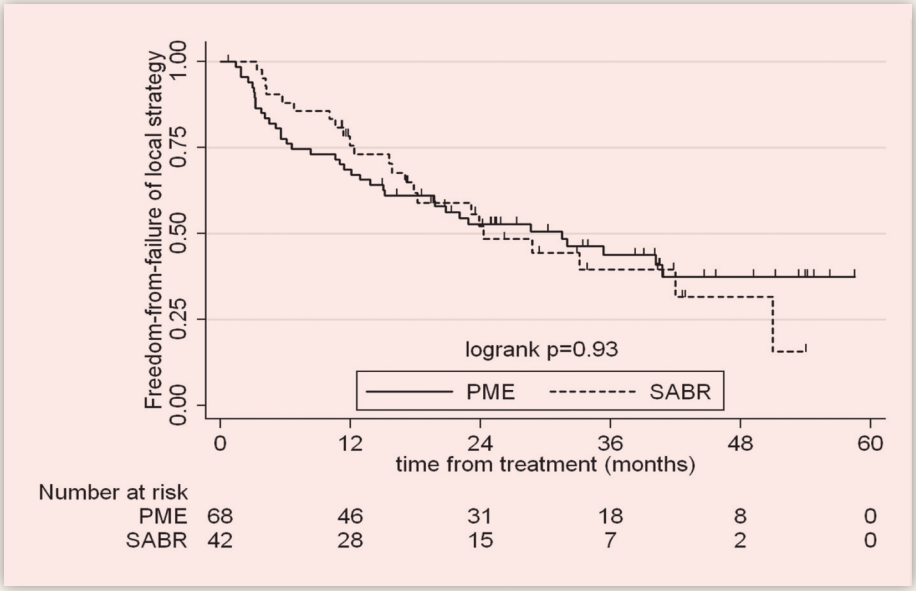
**Table 1A: Univariable Cox regression analysis for overall survival**

| Variable | HR (95 % CI) | p-value |
|---|---|---|
| SABR versus PME | 0.79 (0.43--1.42) | 0.427 |
| Age (per year) | 1.00 (0.98--1.03) | 0.865 |
| Sex (female versus male) | 0.64 (0.36--1.14) | 0.130 |
| Colorectal primary (versus other) | 0.86 (0.49--1.51) | 0.605 |
| Metastases-free-interval (per month) | 0.99 (0.98--1.01) | 0.187 |
| Number of lesions (per lesion) | 1.21 (0.90--1.62) | 0.198 |
| Size of largest lesion (per centimetre) | 0.80 (0.60--1.08) | 0.140 |
| Previous chemotherapy (versus no chemotherapy) | 1.04 (0.54--2.09) | 0.895 |

**Appendix Table 1a.** Univariable Cox regression analysis for overall survival.




**Appendix Figure 1A**: Progression-free survival after index treatment.




**Appendix Figure 2A**: Freedom-from-failure of a local-only strategy (endpoint: no longer amendable for local treatment, i.e. resection, stereotactic radiotherapy, or radiofrequency ablation in the case of hepatic progression).

# Long-term Outcome of Surgery or Stereotactic Radiotherapy for Lung Oligometastases

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## Introduction

Intuition suggests that pulmonary metastasectomy (PME) with clear margins would entail the best odds of cure for patients with limited pulmonary metastases (oligometastases) from solid tumors and is recommended for various malignancies in guidelines. Stereotactic ablative radiotherapy (SABR) is frequently regarded as the second-best option in cases with any arguments against surgery: higher age, compromised physical condition, unfavorable central location of a nodule in the lungs, or higher number of previous metastasis-directed (local) treatments or shorter metastasis-free interval (MFI). Randomized or population-based studies comparing PME with SABR for pulmonary oligometastases are unavailable, as are evidence-increasing comparisons between any local metastasis-directed treatments and systemic approaches or cohorts with long-term follow-up.[1–3]

We present long-term results from our previously published consecutive cohort treated with PME or SABR for pulmonary oligometastases from various cancers.[4] The primary purpose of the present study was to assess long-term overall survival (OS), local recurrence (LR) of treated metastases, progression-free-survival, and time to failure of local-only treatment strategy. In addition, the influence of lesion size of index metastases on survival and local control (LC) was explored in an attempt to gain exploratory information concerning choice of the optimal point in time for local treatment of metastases.

## Methods

All consecutive patients who received a recommendation at our institution's multidisciplinary thoracic tumor board for a local metastasis-directed treatment with curative intent for pulmonary metastases between 2007 and 2010 were included and retrospectively analyzed. Primary tumors and eventual other metastases had been removed in all patients, and the patients received a recommendation for a local-only treatment strategy with curative intention. No patient had received biologically targeted or immune therapy.

The standard first-choice recommendation was to surgically remove all lung metastases. SABR for all lesions was recommended in the case of arguments against surgery, typically consisting of a combination of higher age, compromised physical condition, unfavorable central location of a nodule in the lungs, or a higher number of previous metastasis-directed (local) treatments or shorter MFI. Patients were followed-up at 3- to 4-month intervals with a computed tomography scan of the thorax and abdomen and rediscussed at the tumor board in the case of progression. Survival information was double-checked by family physicians. OS from index treatment to death or last survival information comparing SABR with PME was estimated by using both univariable and propensity score–adjusted Cox regression analysis. The propensity score was based on age, primary tumor, prior chemotherapy, number of prior local treatments for metastases, number of lesions, and MFI (duration from discovery of primary tumor to first detection of any metastases). Cumulative incidence of LR was estimated from index treatment to local failure triggering further treatment at the multidisciplinary conference, with death or failure of local-only treatment strategy constituting competing risks.

As all patients were discussed at the multidisciplinary thoracic tumor board before further treatment; time to failure of local-only treatment strategy was measured from index treatment to board recommendation against further local-only treatment (no matter in which organs the new metastases were located). To estimate the impact on LR or OS of the delay from first detection of an index metastasis to treatment with SABR or PME, we also tested whether these two end points were influenced by lesion size. Lesion size was entered as a continuous variable, so that a hazard rate (HR) higher than 1 would depict worse outcome in larger lesions. The study was approved with an informed consent waiver by the university's institutional review board. Analyses were done with STATA software, version 13 (StataCorp LP, College Station, TX).

## Results

A total of 110 patients were included, and the median follow-up time was 7.6 years (5.8–9.8). The median ages were 70 and 61 years (p < 0.001) for SABR

| Characteristic | PME (n = 68) | SABR (n = 42) | All (N = 110) | *p* Value |
|---|---|---|---|---|
| Male-to-female ratio | 37:31 | 27:15 | 64:46 | 0.308 |
| **Median age (range), y** | 61 (18-80) | 70 (49-89) | 63 (18-89) | **<0.001** |
| **Primary tumor** | | | | **<0.001** |
| Colorectal | 39 (57%) | 31 (74%) | 70 (64%) | |
| Sarcoma | 18 (27%) | 1 (2%) | 19 (17%) | |
| NSCLC | 0 | 6 (14%) | 6 (5%) | |
| Renal | 5 (7%) | 1 (2%) | 6 (5%) | |
| Other | 6 (9%) | 3 (7%) | 9 (8%) | |
| **Median metastasis-free interval (range), mo** | 18.0 (0-138) | 12.7 (0-86) | 15.7 (0-138) | **0.045** |
| No. of lesions | | | | 0.821 |
| 1 | 40 (59%) | 27 (64%) | 67 (61%) | |
| 2 | 21 (31%) | 7 (17%) | 28 (26%) | |
| 3 | 3 (4%) | 7 (17%) | 10 (9%) | |
| 4 | 2 (3%) | 1 (2%) | 3 (3%) | |
| 5 | 2 (3) | 0 (0%) | 2 (2%) | |
| Mean size of largest lesion, cm (95% CI) | 2.0 (1.7-2.4) | 1.7 (1.4-2) | 1.9 (1.7-2.1) | 0.162 |
| **One or more prior metastasis-directed local therapies** | 23 (34%) | 25 (60%) | 48 (44%) | **0.01** |
| **Prior chemotherapy for metastatic disease** | 8 (12%) | 13 (31%) | 21 (19%) | **0.013** |

*Note*: Boldface indicates statistical significance.
PME, pulmonary metastasectomy; SABR, stereotactic ablative radiotherapy; CI, confidence interval.

**Table 1.** Patient, tumor, and pretreatment characteristics.

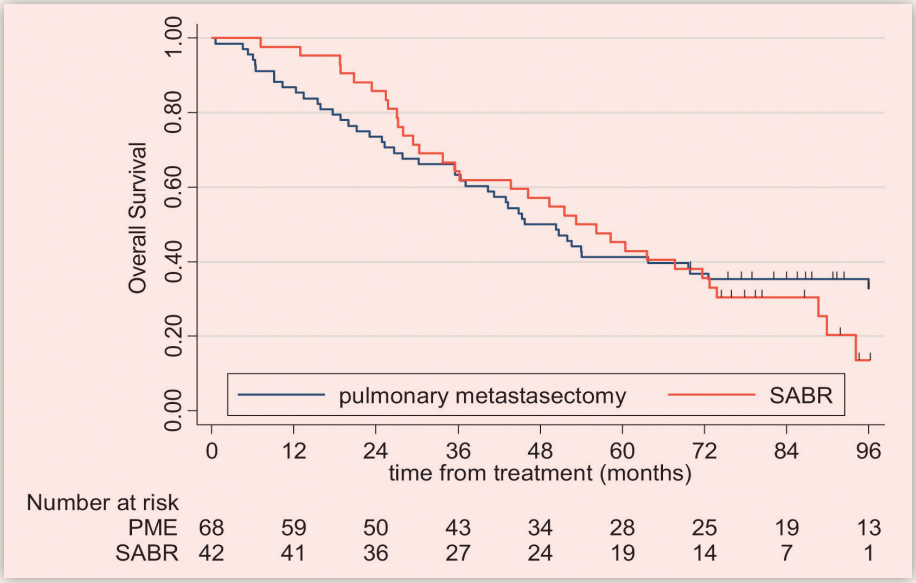


**Figure 1.** Unadjusted overall survival of PME and SABR.

| Characteristic | Percentage and 95% Confidence Interval | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 y | 2 y | 3 y | 4 y | 5 y | 6 y | 7 y | 8 y |
| Overall survival | | | | | | | | |
| PME | 87 (76-93) | 74 (61-82) | 63 (51-73) | 50 (38-61) | 41 (29-53) | 37 (26-48) | 35 (24-46) | 35 (24-46) |
| SABR | 98 (84-100) | 86 (71-93) | 64 (48-77) | 57 (41-70) | 45 (30-59) | 35 (21-50) | 29 (16-44) | 13 (3-30) |
| All patients | 91 (84-95) | 78 (69-85) | 64 (54-72) | 53 (43-62) | 43 (33-52) | 36 (27-45) | 33 (24-42) | 28 (20-38) |
| Freedom from failure of local strategy | | | | | | | | |
| PME | 69 (56-78) | 54 (41-65) | 46 (34-57) | 40 (28-51) | 40 (28-51) | 40 (28-51) | 40 (28-51) | 35 (22-48) |
| SABR | 76 (60-86) | 57 (41-70) | 49 (33-63) | 46 (31-61) | 40 (25-55) | 37 (22-52) | 32 (17-48) | 32 (17-48) |
| All patients | 72 (62-79) | 55 (45-64) | 47 (37-56) | 42 (33-51) | 40 (30-49) | 39 (29-48) | 37 (28-47) | 34 (24-45) |
| Progression-free survival | | | | | | | | |
| PME | 56 (43-66) | 35 (23-46) | 26 (16-36) | 23 (13-33) | 20 (11-30) | 20 (11-30) | 20 (11-30) | 20 (11-30) |
| SABR | 49 (34-63) | 27 (14-41) | 18 (8-32) | 18 (8-32) | 18 (8-32) | 18 (8-32) | 18 (8-32) | 18 (8-32) |
| All patients | 53 (43-62) | 32 (23-40) | 23 (15-31) | 21 (14-29) | 19 (12-27) | 19 (12-27) | 19 (12-27) | 19 (12-27) |
| Freedom from local progression | | | | | | | | |
| PME | 93 (83-97) | 91 (79-96) | 85 (70-93) | 85 (70-93) | 81 (65-90) | 81 (65-90) | 81 (65-90) | 81 (65-90) |
| SABR | 95 (80-99) | 95 (80-99) | 90 (70-97) | 90 (70-97) | 83 (57-94) | 83 (57-94) | 83 (57-94) | 83 (57-94) |
| All patients | 94 (86-97) | 92 (84-96) | 87 (76-93) | 87 (76-93) | 82 (69-90) | 82 (69-90) | 82 (69-90) | 82 (69-90) |

PME, pulmonary metastasectomy; SABR, stereotactic ablative radiotherapy.

**Table 2.** Life tables for PME (n = 68), SABR (n = 42), and all patients (n = 110)

and PME, respectively, and the respective MFI values were 12.7 and 18.0 months (p = 0.045), both disadvantaging SABR (Table 1). Actuarial outcome data are displayed in Table 2, and Figure 1 shows unadjusted OS curves from the date of index treatment. The 5-year OS rates were 45% for patients treated with SABR and 41% after PME, respectively. The unadjusted HR of OS for SABR versus PME was 1.11 (95% confidence interval [CI]: 0.70–1.75); it decreased to 0.76 (95% CI: 0.38–1.54) after propensity score adjustment (neither was significant). The actuarial LR rates at 5 years were 17% for SABR and 19% for PME, and the HR at competing risk analysis for LR was 0.80 (95% CI: 0.24–2.65) for SABR versus PME. Although about half of the patients had progressed by 1 year, rendering progression-free survival rates of 49% and 56% for SABR and PME, respectively, 20% of patients had remained free from any progression at 5 years and 40% had not failed a local-only strategy for management of their metastatic disease at 5 years (see Table 2), meaning that they had not received any systemic treatment since index local treatment.

Lesion size did not influence either LC (HR ¼ 1.03, 95% CI: 0.73 – 1.45) or OS (HR ¼ 0.85, 95% CI: 0.69 – 1.04), but the HR for OS pointed in the direction of more favorable survival with increasing lesion size.

## Discussion

Despite higher age and shorter MFI suggesting higher baseline risk for death after SABR compared with PME, even unadjusted reanalysis at almost 6 years' minimum follow-up time of a consecutive cohort still does not provide an

argument supporting the notion that surgery for pulmonary oligometastases would result in better survival or LC compared with SABR.[4] Although these results must be interpreted with caution on account of the limited sample size, they are strikingly comparable to those of the largest retrospective PME analysis, according to which the 5- and 10-year survival rates were 36% and 26%, respectively.[5] Also, we did not find any signals suggesting that treating smaller rather than larger metastatic lesions would entail more favorable survival or LC, challenging the frequently adhered to notion that local treatment of metastases should be initiated as early as possible. Rather, postponing treatment for asymptomatic metastases detected during follow-up until they are demarcated as truly limited in number could be a reasonable strategy to identify patients with an oligometastatic disease pattern that is likely based on tumor biology and spare from useless local metastasis-directed interventions those patients who would progress to systemic failure anyway at short notice.

We are presently conducting a randomized trial testing the optimal time point of SABR for pulmonary oligometastases from colorectal cancer (NCT02414334). The present analysis does not support favoring surgery over SABR; but still, it also does not provide direct evidence for using either resection or SABR for oligometastases.[1]

Rigorous research comparing a primarily local treatment strategy with nonlocal treatment strategies is urgently needed to better characterize patients who might benefit from aggressive local treatment of lung metastases with the intention of cure or, at least, postponement of systemic treatment for as long as possible.

In addition and complementary to that strategy, in an era of increasing use of molecularly targeted agents and immunotherapy for metastatic disease, there is a need for characterization of situations in which local metastasis-directed treatment would supplement such systemic treatment by effectively tackling localizable treatment resistance.

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# Patterns of Recurrence and Survival after Surgery or Stereotactic Radiotherapy for Early Stage NSCLC

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## Introduction

Lobectomy with systematic lymph node dissection is the standard procedure for medically operable patients with stage I non–small-cell lung cancer (NSCLC), with a 5-year survival of 50% to 70%.[1,2] A considerable part of patients with resectable early stage NSCLC is however medically inoperable because of frailty or severe comorbidity.[3] In a cohort of 10,984 patients with early stage NSCLC, surgery was not performed in 23.3% of the white patients and 36% of the black patients. This included inoperable patients as well as patients refusing surgery.[4] The most common reasons for medical inoperability are poor lung function, which is often seen in COPD patients, or cardiovascular co-morbidity, both of which bring about an increased risk of postoperative pulmonary complications. When withholding inoperable patients any antitumor treatment, the prognosis is poor and most of them will die because of tumor progression. The 5-year overall survival in untreated patients is 6% or less.[3,5]

From the late 1990s, technological improvements of radiotherapy planning software, verification devices, together with advanced planning-CT techniques (4D-CT) made stereo-tactic treatment of small tumor volumes with very high doses per fraction possible. With stereotactic ablative radiotherapy (SABR), higher dose in just a few fractions can be delivered and surrounding tissue is much better spared than with 3D-conformal radiotherapy.[6,7] In patients with stage I NSCLC, overall survival and local control rates after SABR are better compared with rates found after conventional 3D-conformal radiotherapy.[8]

Potential clinical advantages of SABR over surgery are the absence of an invasive procedure with possible associated complications, anesthesia, and hospital admission. However, no randomized trials comparing clinical outcomes after either procedure are available.

Several studies have been performed regarding the effect of SABR on survival and tumor control. Soldà et al.[9] reviewed 45 reports analyzing SABR in patients with stage I NSCLC and found survival rates similar to those in a large matched surgical cohort.

A recent large single-center retrospective study, in contrast, found lower 3-year overall survival rates for SABR compared with surgical patients.[10] Local tumor control after SABR is generally good, with previously reported rates rang-ing between 85% and 98%.[9–14] Few studies were performed comparing the outcomes of a SABR cohort directly with a primarily operable surgical cohort.[10,14–17]

We performed a retrospective study in a large consecutive cohort of patients with clinical stage I NSCLC treated at a single university medical center with surgery or SABR, with the aim to compare survival rates and patterns of tumor recurrence. Comorbidity, age, and performance status were the factors upon which treatment allocation had been based at the multidisciplinary pulmonary oncology panel. Thus, all analyses were adjusted for these factors.

Because of patient selection, we hypothesized a significantly worse unadjusted survival for the SABR cohort that should be equalized after adjustment. Also, we expected comparable adjusted local, locoregional, and distant tumor recurrence rates in the SABR and surgical cohorts using competing risk analysis.

## PATIENTS AND METHODS

### Patients

The study was conducted at the University Medical Center Groningen in the Netherlands. Because all data in this study were obtained from patient medical records and patients themselves were not involved in the study, neither approval of the Institutional Review Board nor informed consent were required according to Dutch law.

All consecutive patients treated between January 2007 and July 2010 with curatively intended surgery or SABR for proven or suspected fluorodeoxyglucose positron emission tomography–computed tomography (FDG-PET–CT)-staged NSCLC were selected from the database.

**Inclusion and Exclusion Criteria**

Patients with cT1-2aN0M0 tumors (less than 50 mm) according to the 7th TNM edition were included[18] (Fig. 1). Staging was based on FDG-PET/CT. Furthermore, inclusion required cytological or histological confirmation of the tumor or, in absence of a pathological confrmation, a combination of imaging information requiring increased FDG-PET-uptake and/or a growing or new lesion on CT exhibiting signs of malignancy. FDG-avid or CT-enlarged (greater than 10 mm short axis diameter) lymph nodes were examined with mediastinoscopy or endosonography with fine-needle aspiration to confirm that their nodes are free of tumor. Patients with a preoperatively proven benign lesion, lung metastases, small-cell lung cancer, or lymph node metastases were not included as well as patients with neoadjuvant

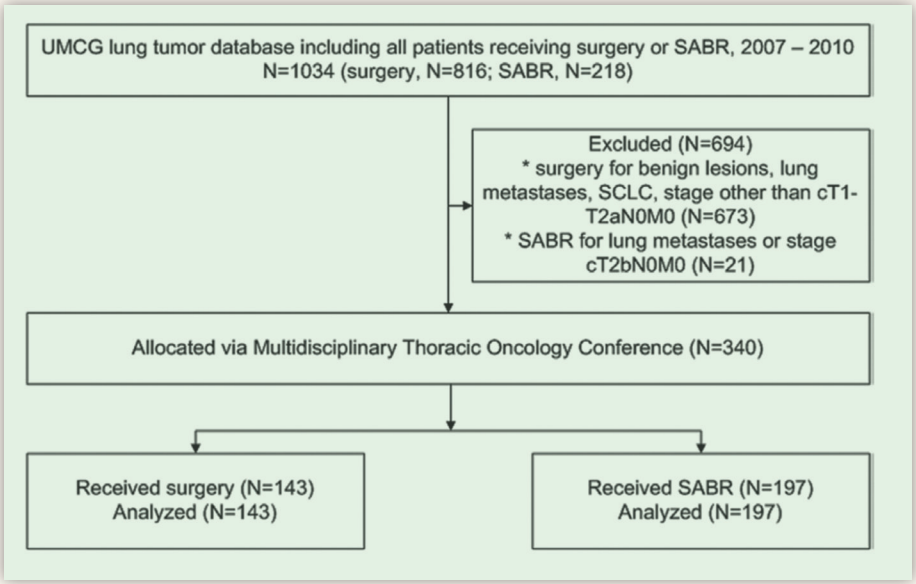


**Figure 1.** Consort diagram.

chemotherapy or radiotherapy (Fig. 1). Patient allocation to treatment required discussion at the multidisciplinary pulmonary oncology panel.

**Treatment Procedures**

Surgery was performed via open thoracotomy (94% of the cases) or video-assisted thoracic surgery and included wedge resection, lobectomy, bilobectomy, or pneumonectomy, the latter three operations with hilar and mediastinal lymph-node dissection. SABR was based on a 4D-planning CT.

The planning target volume (PTV) was defined as the envelope including the moving gross tumor volume plus a margin in all directions of 5 mm. After the institutional protocol, a risk-adapted fractionation schedule of 3 to 12 fractions to 60 Gy was administered using a Novalis accelerator, online position verification and correction was performed using the Exac-Trac system with a 6D-robotic couch (Brainlab, Feldkirchen, Germany).[8] In brief, lesions completely surrounded by lung tissue and not located within 2 cm of the central airways received three fractions of 20 Gy. Lesions located within the 2 cm corridor of trachea and main bronchi received eight fractions of 7.5 Gy or 12 fractions of 5 Gy, whereas lesions adjacent to the thoracic wall received five times 12 Gy. During the study period, a pencil-beam dose-calculation algorithm with tissue heterogeneity correction had been used and the dose was prescribed at 80% isodose comprising periphery of the PTV.[8]

**Follow-Up**

Patient data were extracted from the hospital patient files and supplementary information was retrieved via telephone contact with general practitioners. Patients' vital status was additionally obtained from the Municipal Personal Records Database with a cut off on January 30, 2014. During follow-up, regular CT scans were made to monitor tumor recurrences 3 and 6 months after treatment, then at 6 months intervals until 2 years and yearly thereafter. FDG-PET was only performed when clinically indicated. Tumor recurrence was scored in case of greater than 20% tumor growth (after SABR), new lesions on CT or brain MRI, or a confirmatory FDG-PET showing high FDG uptake in the lesion.

**Study Endpoints**

The endpoints of the study were overall survival and local, nodal, locoregional (=local or nodal or both), and distant tumor recurrence or new pulmonary tumors. To score local recurrence in a study comprising patients with lobectomy, pneumonectomy, wedge resection, and SABR is highly challenging. In this study, local recurrence after both surgery and SABR was defned as a growing tumor in the same lobe as the primary tumor including growth at the irradiated location (the PTV) or around the surgical clips including the ipsilateral hilus. Tumor occurring in another lobe or extrathoracic tumor was defned as distant metastasis. Locoregional tumor recurrence was defined as local recurrence as defined above plus any mediastinal or hilar lymph node metastasis.

**Statistics**

Overall survival was estimated using the Kaplan–Meier method. Time was taken between the date of surgery or the first fraction of SABR and date of

| | Surgery (n = 143) No. of Patients (%) | SABR (n = 197) No. of Patients (%) | p Value |
|---|---|---|---|
| Age, years | | | <0.001 |
| Median | 67 | 77 | |
| Range | 40–84 | 52–93 | |
| Sex | | | NS |
| Men | 96 (67) | 143 (73) | |
| Women | 47 (33) | 54 (27) | |
| WHO performance score | | | <0.001 |
| 0–1 | 143 (100) | 155 (79) | |
| 2–3 | 0 (0) | 42 (21) | |
| Charlson comorbidity index | | | 0.012 |
| Median | 2 | 2 | |
| Range | 0–5 | 0–5 | |
| 0–1 | 65 (45) | 77 (39) | |
| ≥2 | 78 (55) | 120 (61) | |
| Current or former smoker | 124 (87) | 195 (99) | <0.001 |
| cTNM classification | | | NS |
| cT1aN0M0 | 61 (43) | 71 (36) | |
| cT1bN0M0 | 22 (15) | 55 (28) | |
| cT2aN0M0 | 60 (42) | 71 (36) | |
| Tumor size in mm, median (range) | 23 (5–50) | 25 (5–50) | NS |
| Tumor location | | | NS |
| Right upper lobe | 51 (36) | 73 (37) | |
| Right middle lobe | 9 (6) | 9 (5) | |
| Right lower lobe | 25 (18) | 26 (13) | |
| Left upper lobe | 36 (25) | 55 (28) | |
| Left lower lobe | 22 (15) | 34 (17) | |
| Surgical treatment | | | |
| Pneumonectomy | 5 (3) | | |
| Lobectomy | 110 (77) | | |
| Bilobectomy | 11(8) | | |
| Wedge resection | 17 (12) | | |
| pTNM classification | | | |
| pT1aN0M0 | 50 (35) | | |
| pT1bN0M0 | 23 (16) | | |
| pT2aN0M0 | 30 (21) | | |
| upstaged to >stage I: | 35 (24) | | |
| pT1a-2aN1M0 | 16 (11) | | |
| pT1a-2aN2M0 | 11 (8) | | |
| pT2bN0-2M0 | 8 (6) | | |
| Other tumor[a] | 2 (1) | | |
| Benign[b] | 3 (2) | | |
| SABR schedule | | | |
| 3×20 Gy | | 95 (48) | |
| 5×12 Gy | | 59 (30) | |
| 8×7.5 Gy | | 39 (20) | |
| 12×5 Gy | | 4 (2) | |
| Follow-up time, months | | | NS |
| Median | 61 | 61 | |
| Range | 43–84 | 43–79 | |

[a]One melanoma; one salivary gland tumor.
[b]One solitary fibrous tumor; two localized infections.
WHO, World Health Organization; SABR, stereotactic ablative radiotherapy; NS, not significant.

**Table 1.** Demographic, clinical, and treatment characteristics of included patients (n = 340).

death because of any cause or most recent date alive. To determine the role of covariables on overall survival, Cox regression analyses were performed. The following covariables were analyzed: treatment, age, sex, WHO performance score, Charlson comorbidity index, and tumor size. Significant factors were included in the multivariable models. For tumor recurrences and metastases, multivariable competing risk analyses with death and nontarget-type (first) recurrences as competing risk were performed. With this method, it is possible to correct for differences in inter-current death and censoring because of clinical necessities. For example, occurrence of distant metastases was a competing risk for local recurrence, because imaging to identify local recurrence had been ceased in these patients. Thus, they were no longer at risk for local recurrence, a fact that is neglected in e.g., Cox regression analysis.

## RESULTS

### Patient, Tumor, and Treatment Characteristics

A total of 340 patients treated with surgery (n = 143) or SABR (n = 197) were included. Patient and treatment characteristics are shown in Table 1. Patients treated with surgery were 10 years younger, had a better performance status, less comorbidity, and better lung function tests, but tumor size and clinical stage were not different. FDG-PET/ CT was used for staging in all patients, endoscopic ultrasound and cervical mediastinoscopy were only used in 1% and 4%, respectively. Of note, in 85 of the surgical patients(59%), no tumor tissue had been obtained before surgery, although in 59 of them (69%) one or more biopsies had been attempted. In 154 of the SABR patients (78%), no tumor tissue was obtained.

Significantly more patients in the surgical cohort had an FDG-negative primary tumor ($p < 0.001$). The indication for resection in these cases had been based on spiculation and tumor growth on repeated CTs.

For surgical patients, the median hospital stay was 9 days with a range of 3–111 days; in 90% of the patients, admission was less than 25 days. Stereotactic radiotherapy was exclusively administered in an outpatient setting.

In the surgical cohort, 15% of the patients received adjuvant chemotherapy and 2% had postoperative radiotherapy for incomplete resection. Only a single patient (less than 1%) had adjuvant chemotherapy after SABR ($p < 0.001$).

### Overall Survival

Median follow-up was 61 months. Age, performance status, comorbidity, tumor size, and treatment (surgery better than SABR) were highly significant predictive factors for survival at univariable analysis. After adjustment for

the former factors, the difference in survival between surgery and SABR disappeared and the adjusted SABR versus surgery hazard ratio (HR) for overall survival was 1.07 (95% confdence interval [CI]: 0.74–1.54; p = 0.73). Of note, adjuvant therapy was not signifcantly related to overall survival. Unadjusted survival rates are shown in Table 2.

**Tumor Recurrences and Occurrence of New Primaries**

Local tumor control using the definition as described above was not different between SABR and surgery (adjusted sub-HR 1.21; 95% CI: 0.38–3.90; p = 0.75). Also for distant recurrence, no significant difference was found between both treatments (adjusted sub-HR 1.01; 95% CI: 0.56–1.84; p = 0.97). Treatment was not a significant factor for nodal tumor recurrence, but a trend for more nodal recurrences after SABR was found (adjusted sub-HR 2.17; 95% CI: 0.91–5.17; p = 0.079).

| | 1 Year | 2 Years | 3 Years | 5 Years |
|---|---|---|---|---|
| Overall survival | | | | |
| Surgery | 91.6 | 80.4 | 68.5 | 58.2 |
| SABR | 88.3 | 76.6 | 56.9 | 31.8 |
| Free from local recurrence | | | | |
| Surgery | 98.3 | 97.2 | 96.0 | 93.0 |
| SABR | 98.9 | 95.9 | 95.1 | 80.0 |
| Free from lymph node recurrence | | | | |
| Surgery | 97.4 | 92.4 | 90.1 | 87.3 |
| SABR | 92.0 | 88.3 | 88.3 | 78.7 |
| Free from locoregional recurrence | | | | |
| Surgery | 97.4 | 92.4 | 90.1 | 87.3 |
| SABR | 90.9 | 85.6 | 84.8 | 77.2 |
| Free from distant recurrence | | | | |
| Surgery | 89.9 | 82.7 | 76.8 | 74.1 |
| SABR | 91.5 | 85.0 | 80.6 | 65.9 |
| Free from any recurrence | | | | |
| Surgery | 89.1 | 82.7 | 76.8 | 71.7 |
| SABR | 84.7 | 77.8 | 72.7 | 57.4 |

Locoregional recurrence = local or lymph node or both.
SABR, stereotactic ablative radiotherapy.

**Table 2.** Unadjusted survival and freedom-from-recurrence rates (%).

Locoregional recurrences however -local or nodal or both together- were significantly more frequent after SABR compared with surgery (adjusted sub-HR 2.51; 95% CI: 1.10– 5.70; p = 0.03; Fig. 2).

Nodal and distant metastases, but not local recurrence, were significant independent predictive factors for survival (Table 3). The gross pattern of recurrence is displayed in Table 4. Unadjusted freedom-from-tumor-recurrence rates are shown in Table 2.

## DISCUSSION

For medically inoperable patients with early stage NSCLC, SABR has evolved as the preferred treatment option.[19,20] There are no randomized comparative trials available comparing surgery with SABR. However, such trials would by definition be confined to operable patients. Therefore, the evolution of SABR has been mainly triggered by promising results for local tumor control after SABR. [9–14,21] The range of reported survival rates after SABR is understandably variable because of patient selection.[9] Moreover, little is known about the reasons for decreased survival after SABR: is it mainly because of comorbidity prompting medical inoperability, or is it because of differences in patterns of recurrence, or to both factors. To date, few studies have accepted the challenge to compare the outcomes of a SABR cohort directly with a surgical

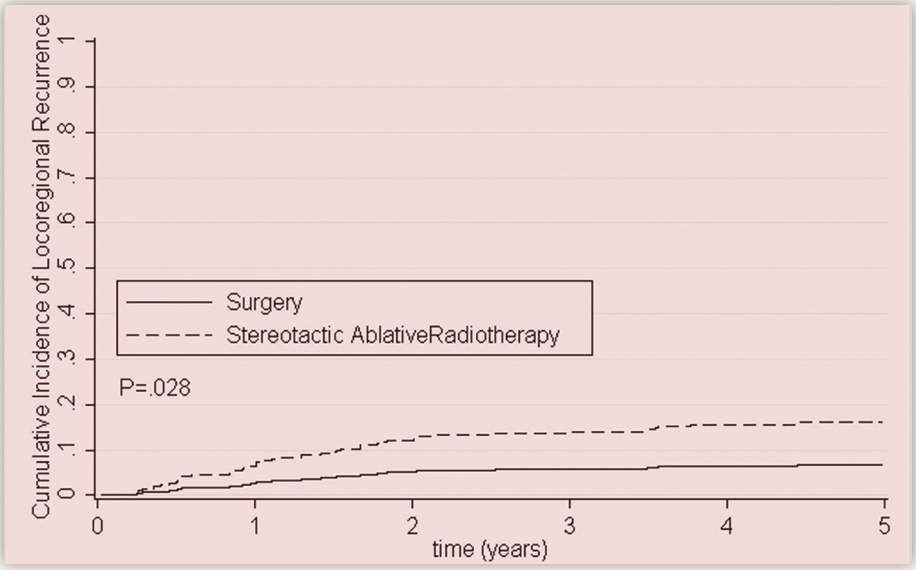


**Figure 2.** Cumulative incidence of locoregional failure after surgery or stereotactic radiotherapy based on competing risk analysis.

cohort. [15–17,22] Typically, younger and fitter patients with less comorbidity and better lung function are offered surgery for solitary FDG-positive lung lesions highly suspicious for NSCLC, whereas the medically marginally operable or inoperable patient is offered SABR. In the absence of randomized data, comparative survival and recurrence data corrected for these well-known selection parameters are the second best source to possibly inform clinical decision making. To analyze survival rates, patterns of tumor recurrence after surgery or SABR, and the impact of recurrence patterns upon survival, we studied a consecutive cohort of patients with *c*T1-2aN0M0 lung tumors highly suspicious for NSCLC. Our hypothesis was that SABR, when adjusting for group differences, would be equally effective as surgery in terms of tumor control and survival.Our study indeed showed that survival depended on age,

| Variable | Hazard Ratio | 95% CI | pValue |
|---|---|---|---|
| Age, per year | 1.041 | 1.02–1.06 | <0.001 |
| Charlson comorbidity index,≥2 vs. 0–1 | 1.453 | 1.07–1.98 | 0.017 |
| WHO performance score, ≥2 vs. 0–1 | 2.025 | 1.35–3.04 | 0.001 |
| Tumor size, per mm | 1.013 | 1.00–1.03 | 0.061 |
| Treatment, SABR vs. surgery | 0.98 | 0.68–1.41 | 0.915 |
| Local recurrence | 0.996 | 0.53–1.89 | 0.991 |
| Lymph node recurrence | 2.163 | 1.34–3.48 | 0.002 |
| Distant recurrence | 2.123 | 1.52–2.97 | <0.001 |

**Table 3.** Multivariable Cox-model of factors predicting overall survival

performance status, comorbidity, and tumor size, and that adjusted overall survival after surgery or SABR was not different. Prospective single arm trials involving SABR and retrospective analyses comparing SABR with surgery have found similar overall survival rates as we have found in our study. [10–12,23] A recently published review showed even similar 2- and 3-year overall survival rates after SABR and surgery.[9] Also, the largest retrospective single-center SABR analysis showed comparable survival and recurrence rates.[21]

Lagerwaard et al.[13], who analyzed potentially operable patients having received SABR, found higher overall survival rates compared with our study because of selection of a fitter patient group. An even higher 5-year overall survival of 69.5% was found by Onishi et al .[24], however, this was a cohort of 87 medically operable Japanese patients treated with SABR, who show better survival very consistently in most studies involving lung cancer.

In our study, we defined local tumor recurrence as recurrence in the same lobe as the primary tumor or at the ipsilateral hilus, and locoregional recurrence as including in addition the contralateral hilus or any mediastinal

lymph node metastases. Tumor recurrence definitions are not used consistently in the literature. In most stereotactic radiotherapy or local-and-limited resection studies, local recurrence is defined more restrictive as recurrence at the exact location of the primary tumor .[23] Such a definition precludes reasonable comparisons with lobectomy series. In our study, no

| | Surgery | SABR |
|---|---|---|
| | (n = 143) | (n = 197) |
| Type of Recurrence | No. of Patients (%) | No. of Patients (%) |
| Local | 6 (4) | 11 (6) |
| Lymph node | 12 (8) | 25 (13) |
| Local or node or both | 12 (8) | 30 (15) |
| Distant | 29 (20) | 41 (21) |
| Any | 31 (22) | 57 (29) |
| No recurrence | 112 (78) | 140 (71) |

Local, recurrence in lobe of primary tumor or ipsilateral hilus; lymph node, recurrence in any hilar or mediastinal lymph node; local or node or both = locoregional; distant, recurrence outside locoregional region; any, any of the above recurrence types.
SABR, stereotactic ablative radiotherapy.

**Table 4.** Patterns of failure per treatment group (n = 340).

difference between the treatment groups was found for local recurrence (using our definition) or distant metastases. In contrast to other studies that found no increased locoregional recurrence rate after SABR compared with resection,[16,22] we observed a trend toward more nodal recurrences after SABR and significantly more locoregional tumor recurrences after SABR compared with surgery. In keeping with this result, 24% (19% were solely because of hilar and/or mediastinal lymph nodes) of our FDG-PET-CT-based clinical stage I patients were upstaged postoperatively to higher stages based on the resected specimen (Table 1). This seems to be quite high and may partly be because of an earlier generation PET machine that was used during the time of the study, but it is in line with recent data in the literature. [16,25,26] This stresses the importance of optimal lymph node staging especially if the nodes are not sampled at treatment (i.e., SABR or wedge resection). Even though our patients had undergone FDG-PET, still a number of them will have harvested latent metastases in hilar or mediastinal nodes, which were not treated with SABR. A major argument for surgery thus remains the remaining uncertainty

about hilar (or mediastinal) lymph node involvement despite negative CT and FDG-PET scans. It is well known that small lymph node metastases are not detected by PET. A recently published study showed that the sensitivity, specificity, and accuracy of 18F-FDG-PET/ CT for assessing mediastinal lymph node metastasis with a short-axis diameter of less than 15 mm is still limited.[27] As high as 18% of occult lymph node metastases in an FDG-negative hilus and mediastinum were found in another recent study, and SUV and size of primary tumor were factors predicting node-positivity.[28] Therefore, to improve locoregional tumor control in patients with stage I NSCLC who are eligible for SABR, using new-generation PET and even minimally invasive mediastinal staging using E(B)US with fine needle aspiration or even mediastinoscopy should be carefully considered to spare them potential undertreatment because of neglect of nodal metastases.

A limitation of our study is its retrospective design. However, we double-checked data using information from the general practitioner and the Municipal Personal Records Database in addition to patient files. A serious limitation of the Charlson comorbidity score is that no distinction is made in severity of the comorbidity, e.g., between mild or severe pulmonary problems. Another limitation is because of use of an out-dated radiation dose calculation algorithm during the study period (pencil-beam calculation with heterogeneity correction). Nowadays, Monte Carlo or collapsed cone algorithms are used resulting in higher SABR doses compared with the doses actually delivered during the studied period. Therefore, locoregional tumor control with SABR might have improved in the last couple of years. The strength of this study is the direct comparison of both survival and patterns of tumor recurrence between a large surgical and a large SABR consecutive cohort with a very long follow-up. Indications were discussed at a multidisciplinary tumor board, all patients were staged with FDG-PET/CT, and analyses were based on clinical, not postoperative pathological staging information, which would skew the comparison. Analyses were corrected for the factors upon which patient selection for treatment had been performed and patterns of recurrences were analyzed taking competing risks into account. In conclusion, patients with NSCLC at clinical stage I treated with surgery were 10 years younger, fitter and had less comorbidities than those treated with SABR. Adjusted overall survival was similar between surgery and SABR, but SABR yielded worse locoregional tumor control compared with surgery. This was because of more nodal failures after SABR compared with surgery. SABR is a tailor-made treatment for patients unfit for surgery, but optimal mediastinal and hilar staging remains essential for optimizing treatment decisions.

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# Borderlands of Thoracic Neoplasms

**Cardiac paraganglioma originating from the right coronary artery**

**-**

**Cardiac dynamic magnetic resonance of a giant lung carcinoma invading the left atrium: do not let the imaging fool you.**

**-**

**A 20-year-old male with thoracic pain and a lower thoracic mass**

**-**

**Removal of a giant intrathoracic cyst from the anterior mediastinum**

**-**

**Axillary Chest Wall Hibernoma with intrathoracic extension and presenting as Thoracic Outlet Syndrome**

**-**

**Hybrid Bronchoscopic and Surgical Resection of Endotracheal Angiomatoid Fibrous Histiocytoma**

# Cardiac paraganglioma originating from the right coronary artery

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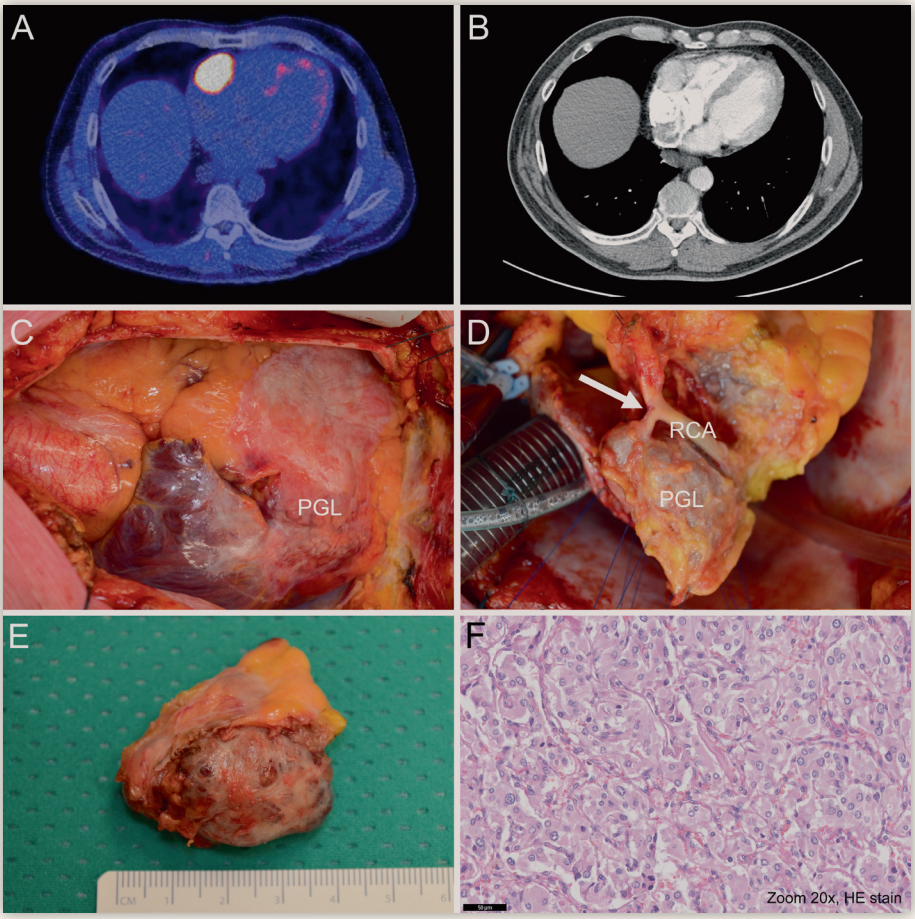


**Figure 1**: 59-year-old man with cardiac paraganglioma (18F-DOPA-PET in **A**; CT in **B**) and elevated plasma normetanephrine underwent resection. Vascularization from the right coronary artery (RCA) (**C,D**) was clipped and transected (**E,F**). Recovery was uneventful. Cardiac paraganglioma are rare and no cases have been described with direct vascularization from the RCA. DOPA: dihydroxyphenylalanine; PET: positron emission tomography; CT: computed tomography; PGL: paraganglioma.

# Cardiac dynamic magnetic resonance of a giant lung carcinoma invading the left atrium: do not let the imaging fool you

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**CASE REPORT**

A 70-year old man with a persistent cough and dyspnoea since a few days ago was referred to the University Medical Center Groningen. He had a positive family history of lung cancer and a history of smoking. Physical examination showed no abnormalities and no signs of cardiopulmonary failure were found. Laboratory findings were unremarkable, with a normal inflammatory state (C reactive protein and leucocytes). The chest X-ray showed a conspicuous right pleural effusion and was followed by a chest computed tomography (CT), which revealed an enormous tumour originating from the lower lobe of the right lung extending into the left atrium of the heart. The first probable diagnosis was non-small-cell lung cancer (NSCLC) from the right lower lobe with direct invasion, through the pericardium and atrial wall, into the atrium and which was hence unresectable. Cytology from needle biopsy confirmed NSCLC: pleiomorph carcinoma of the lung.

On whole-body positron emission tomography scan, there was no evidence of distant metastasis (Fig. 1A), hence it was staged as local advanced disease. The pulmonologist was hesitant to administer chemotherapy because of the high risk of massive tumour embolization, hence local control by surgery was considered, with the hypothesis: 'direct "mushroom-like" growth of the tumour from the lower lobe through the lower pulmonary vein, into the left atrium'.

Although static CT offered high-definition images, these were insufficient for decision-making (Fig. 1B). Therefore, dynamic cardiac magnetic resonance was performed. This clearly showed the absence of tumour invasion into the wall of the pulmonary vein and the left atrium, and the patient was accepted for surgery. The transoesophageal echocardiography (TEE) performed in the operating room showed the left atrium completely occupied by the tumour protruding through the mitral valve.

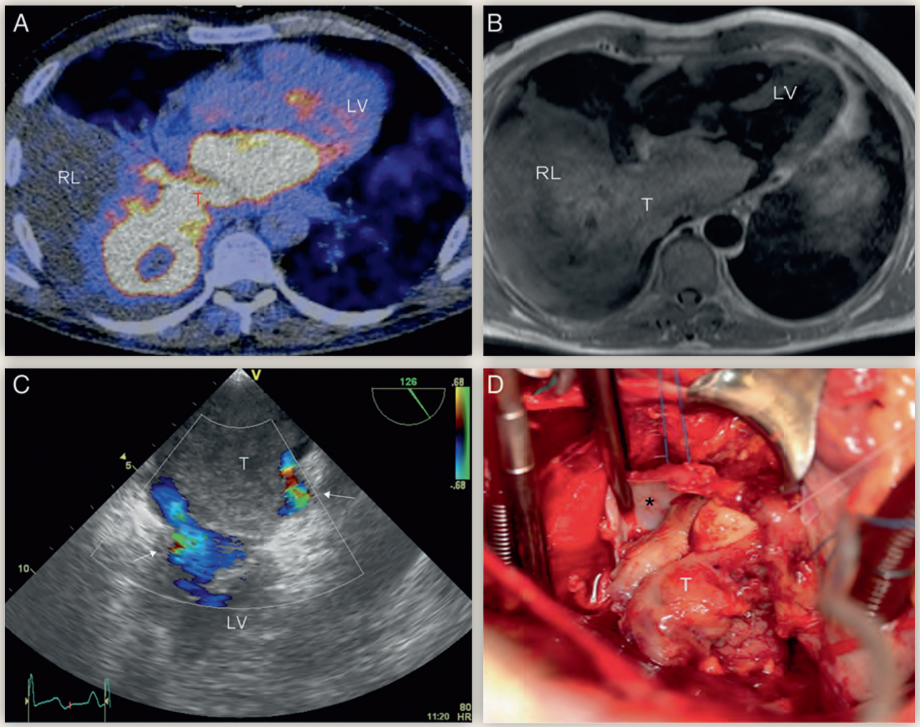


**Figure 1**: (A) FDG (fluorodeoxy-glucose-18) PET-CT scanning (transverse section, four-chamber view) revealed hypermetabolic uptake of FDG in the tumour, consistent with malignancy. (B) Static cardiac MRI imaging did not provide complete information concerning the attachment of the tumour (T) along its tracking into the wall of the pulmonary vein. RL: right lung; LV: left ventricle. (C) The presence of flow at Doppler between the mass and the wall of the left atrium (white arrows) suggests the absence of tumour invasion. (D) The intraoperative detachment of the tumour (T) from the inferior pulmonary vein (*), at the level of the ostium in the left atrium

The presence of Doppler colour flow, between the mass and the wall of the left atrium, also suggested the existence of a virtual space but could not rule out any other possible invasion into the wall of the chamber and pulmonary veins (Fig. 1C).

Surgery was performed through a median sternotomy with cardioplegic arrest of the heart, in a one-stage operation. The roof of the left atrium was opened with extension into the interatrial septum to consider resectability. The hypothesis was confirmed. The tumour extended 'mushroom-like' from the right lower pulmonary vein with macroscopical extension through the atrial wall towards the upper right pulmonary vein (Fig. 1 D). For local control, a right pneumonectomy had to be performed with careful luxation of the tumour mass (diameter 7.8 cm), from the left atrium.

The postoperative period was uneventful, and the patient was discharged 10 days after surgery, and accepted for adjuvant chemotherapy. Postoperative staging was pT4N2M0 (Stage 3b).

## DISCUSSION

To the best of the authors' knowledge, this is the first case reported in the literature in which a dynamic magnetic resonance imaging made the difference in decision-making for surgical resectability of NSCLC with circulatory extension into the heart. Static imaging like CT and MRI did not provide reliable information concerning the growth of the tumor within the heart, which is a dynamic organ. In this challenging clinical case, static imaging only would have led to refusal of surgical treatment, while surgical treatment is still the treatment of choice for NSCLC without distant metastasis[1,2].

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# A 20-year-old male with thoracic pain and a lower thoracic mass

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**CASE REPORT**

A 20-yr-old Caucasian male construction worker had a previous history of a road traffic accident 3 years before presentation. A computed tomography (CT) scan of the thoracic spine was carried out to exclude vertebral damage. No evidence of vertebral bone damage or other lesions was seen, and the patient recovered without sequelae.

A week before presentation, he noticed a stabbing pain in his right hemithorax, without dyspnoea. The pain persisted, and the patient was referred, by his general practitioner, for a chest radiograph (fig. 1).

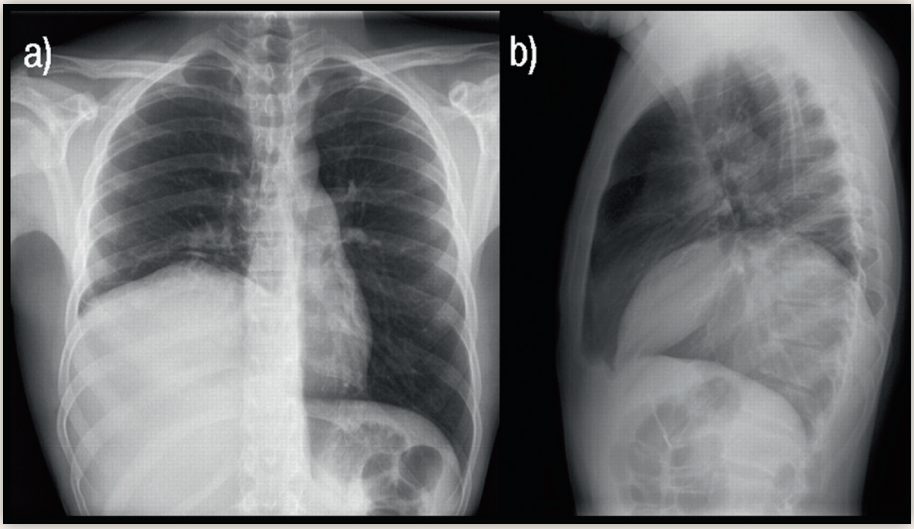


**Figure 1.** a) Postero-anterior and b) lateral chest radiographs at presentation.

Based on these results, the patient was referred to a general hospital for further diagnostic tests. A CT scan of thorax and abdomen (not shown) revealed a large mass, which was interpreted to arise in the right upper abdomen, probably originating from the liver. A malignant tumour, or a metastatic lesion, was suspected and the patient was referred to University Medical Center Groningen (Groningen, The Netherlands).

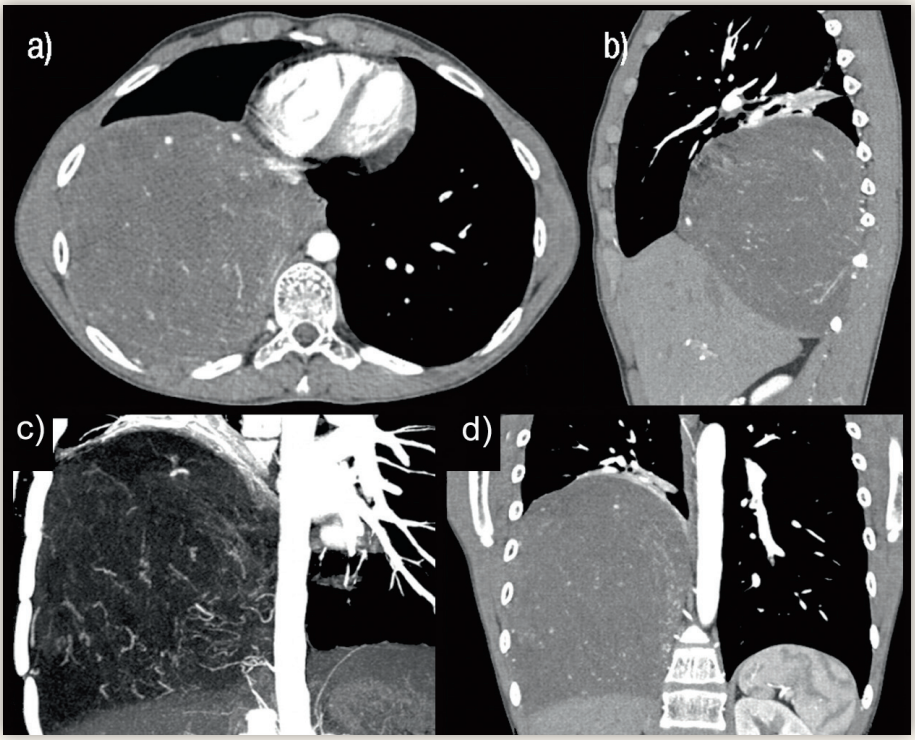


**Figure 2**. Computed tomography angiography of thorax and upper abdomen. Representative images are shown in **a**) transversal, **b**) sagital, and **c** and **d**) frontal views. A computed MIP-reconstruction is shown in **c**.

The patient did not suffer from dyspnoea, cough or haemoptysis and there was no history of fever, weight loss, fatigue or gastrointestinal complaints. The patient was a non-smoker, and did not use any medication.

On physical examination, a healthy appearing, haemodynamically stable young male, of normal posture was seen. On percussion, a dull sound was found in the right lower zone of the chest. Auscultation revealed normal cardiac sounds without murmurs, and normal breathing sounds on the left side and upper right side of the chest. Abdominal examination revealed no

palpable masses or other abnormalities. No palpable lymph nodes were present. Additional physical examination revealed no other abnormalities.

Laboratory tests only showed a slightly elevated serum alkaline phosphatase of 174 U/L-1 (normal value: 13– 120 U/L-1). Serum lactate dehydrogenase, a-fetoprotein and b-human chorionic gonadotropin values were all normal; therefore, an extra-gonadal germ cell tumour was unlikely.

On revision of the CT scan, there was doubt regarding the hepatic origin of the mass. Therefore, abdominal ultrasonography was performed. No focal lesions in the liver parenchyma were observed, and the liver blood flow appeared intact. In the right thoracic region, a mass was seen with variable echogenicity and rich vascularisation. Due to the high degree of vascularisation observed on the abdominal ultrasono-graphy, no percutaneous biopsy was performed.

A CT angiography was performed: first, to narrow the differential diagnosis, and, secondly, to provide the thoracic surgeon with more detailed information about vascularisation (fig. 2). At bronchoscopy, no endobronchial abnormalities were seen. Cytological examination of the bronchial lavage showed no signs of malignancy. A bone scan was normal.

Exploratory thoracotomy revealed a tumour originating from the right dorsal region, lateral from the vertebral column. The surgeon was able to remove the tumour (figs 3 and 4).

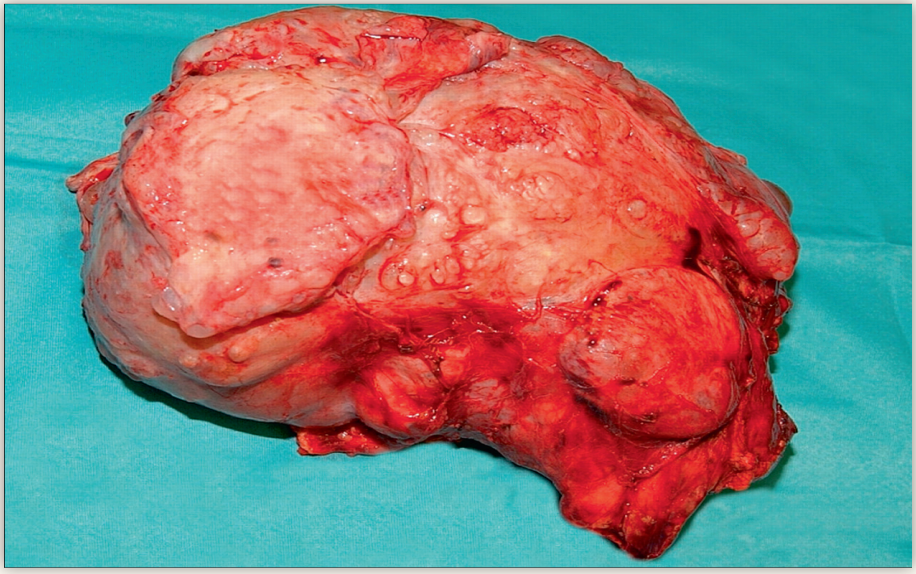

**Figure 3**. Resection specimen.

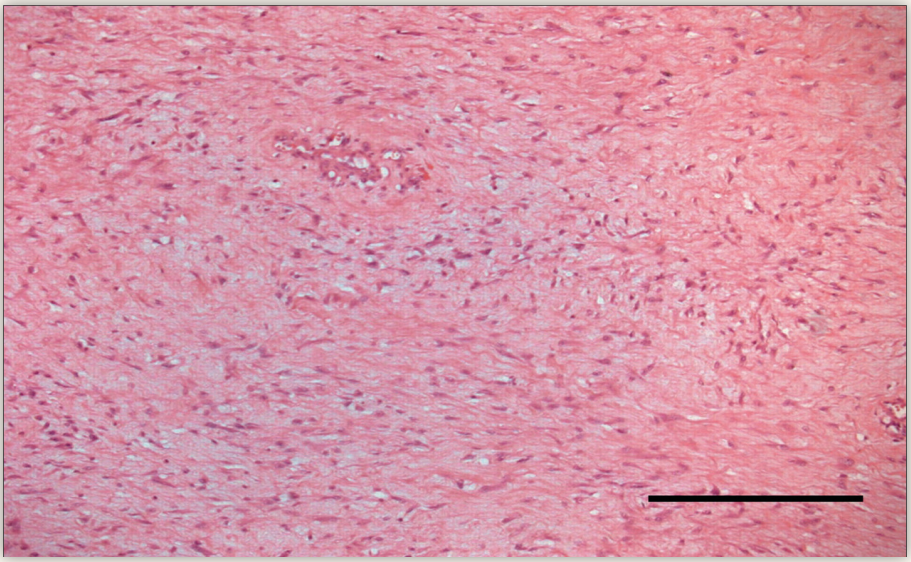

**Figure 4**. Representative microphotograph of the tumour with haematoxylin-eosin staining. Scale bar = 200 µm.

## INTERPRETATION

**Chest radiograph at presentation**
The chest radiograph showed a loss of volume of the right lung (fig. 1). On the lateral view, the density extending from the right posterior ribs does not reach the sternum, suggesting a supradiaphragmatic lesion.

**Computed tomography angiography**
In the right hemithorax, a relatively hypodense mass with large blood vessels was seen, compressing the normal lung and displacing the right hemidiaphragm caudally (fig. 2). A relationship with the thoracic aorta could not be seen, nor any aberrant artery, suggesting a lung sequestration. Blood vessels originated from the intercostal arteries. No enlarged lymph nodes or suspect metastatic lesions were found.

**Resection specimen**
At examination, the tumour weighed 1,700 g, with recon-structed dimensions of 19 x17 x6 cm with a resected peduncle of 6 x4 cm, visible on the right lower side (fig. 3). The tumour had a lobular aspect, and was surrounded by a thin membrane with small fluid-filled cysts.

**Histology**
Microscopy evaluation was used to diagnose a mesenchymal tumour with small spindle cells with some variation in shape, but without atypia, mitotic figures or other malignant characteristics in a fibrous background (fig. 4). The tumour extended into the surgical margins of the resected peduncle.
Using immunohistochemistry, tumour cells were only positive for vimentin, and lacked CD34, S-100, ALK-1, Bcl-2, cytokeratins, actin and desmin staining. Few positive nuclei were seen using Ki-67 staining. The morphology, in combination with immunophenotype, is compatible with a desmoplastic fibroma of the pleura, also known as a desmoid tumour.

**Diagnosis: Intrathoracal desmoid tumour with microscopically incomplete resection.**

**Clinical course**
Although the resection was microscopically incomplete, the patient was not treated with additional surgery or adjuvant radiotherapy (see Discussion). Instead, regular magnetic resonance imaging (MRI) examinations were applied to observe any local recurrence. During 18 months of follow-up, consecutive MRIs did not show any sign of recurrence. The patient has recovered without sequelae and has caught up with his daily work.

## DISCUSSION

Desmoid tumours, also known as aggressive fibromatosis, are slowly growing fibroblastic neoplasms arising from fibroblastic stromal elements. Although desmoid tumours do not metastasise, they tend to be locally invasive. The aetiology is not exactly known, but the association with familial adenomatous polyposis coli (FAP), as well as with previous trauma, has been extensively described[1,2].

Desmoid tumours are very rare; the incidence is between 2–4 per million[3]. The primary location for desmoid tumours is extra-abdominal, with the limb girdle and extremities most commonly involved, followed by the chest wall[4]. Abdominal wall desmoid tumours are mostly seen in females, especially during pregnancy[5]. Intra-abdominal desmoids are seen in correlation with FAP. Slightly more females than males are affected. The age at diagnosis is usually between 15–60 years.

The present study reports a case of a large intrathoracal desmoid tumour. This type, and more so the pleural origin, is very rare and has been reported in 20 cases[6]. There may be a relationship with the traumatic chest injury which the patient suffered 3 years prior to presentation.

The initial differential diagnosis of large, pedunculated, intrathoracal tumours includes both mostly benign and, less frequently, malignant lesions. The most frequent malignant pleural tumour is malignant mesothelioma, which is, in general, a diffuse pleural proliferation and hardly ever presents as a pedunculated mass. Although in the past, several entities were included in the group of mesotheliomas, at present the designation mesothelioma is used for neoplastic proliferation of mesothelial cells and not for proliferation of other cells of the pleura[7]. In this case study, there were no indicators for malignancy, considering the complete lack of atypia and the scarcity of mitoses. This morphology, together with negative cytokeratin staining, makes a diagnosis of mesothelioma unlikely. Consequently, a malignant solitary fibrous tumour of the pleura, recently presented in an article in the European Respiratory Journal, could also be excluded on the basis of morphology and immunohistochemistry[8].

With respect to benign tumours to be considered in the differential diagnosis, a schwannoma of the paravertebral nerves could be excluded on clinicopathological grounds, as absence of relations to intervertebral structures and the negative S-100 staining[9]. A pulmonary sequestration was unlikely, due to anatomical presentation[10]. A solitary fibrous tumour (SFT), developing from the pleura, belongs to the differential diagnosis. Obsolete and confusing terms for SFT are localised or benign fibrous mesothelioma or benign localised fibroma[11]. A vascular peduncle may be present, especially in larger SFTs[12]. The morphology and the negative CD34 and Bcl-2 immunostaining made this diagnosis unlikely[13,14]. The morphology of the tumour, together with the distinctive immunohistochemical results, was compatible with a desmoid tumour.

The primary management of a desmoid tumour consists of complete resection. For patients deemed inoperable, primary radiotherapy treatment is a curative option. In two recent large series, no difference was observed in disease-free survival between microscopically positive and negative resection margins after primary resection[4, 15]. However, some older and smaller studies showed a small decrease in disease-free survival time for microscopically positive margins as compared with disease-free resection margins[16]. Despite complete resection, the rate of local recurrence is ,30%[16]. Most local recurrences develop within 2 years after resection, but a time to recurrence of 10 years has also been described[15].

The use of radiotherapy as adjuvant therapy is, as yet, not substantiated. For incomplete resected tumours, the recurrence rate decreases from 39 to 25% after adjuvant radiotherapy, as was presented in a review by NUYTTENS et al.[16]. Adjuvant radiotherapy was not a predictor for disease-free survival in other studies[4,15]. Moreover, radiation-related complications, such as radiation pneumonitis, soft tissue necrosis and/ or fibrosis, secondary malignancies and skin problems are well known. The application of radiotherapy for incomplete

resection, therefore, remains an issue for debate. The current authors chose not to let the patient be irradiated and to follow-up the patient clinically and radiologically.

Local recurrence can be treated with re-operation or local radiotherapy. In cases with incomplete resection the radiation dose should be X50 Gray to decrease the risk of local recurrence[17]. The disease-free survival for patients with recurrent disease is less than that for primary desmoid tumours[15].

The benefit of additional surgery in case of positive margins is doubtful. Hence, gain in survival has not been demonstrated to be related to negative margins. Therefore, extensive surgery can be postponed until the presence of recurrent lesions[15].

Early detection of tumour relapse gives a higher chance of non-mutilating surgical resection. Follow-up should be performed with a sensitive imaging technique. MRI was preferred in the patient, as it is very specific for detecting slight differences of density between desmoid tumours and surrounding structures. Baseline MRI was chosen to be carried out at 3 months after the operation, because the clips left at operation needed to be firmly grown into the surrounding tissue. As desmoid tumours are slowly growing, 3-month intervals between MRI's were considered appropriate during the first 2 years, after which the intervals will become larger. At present, 18 months after diagnosis, the patient is in an excellent condition and there are no signs of relapse.

In conclusion, a patient with a large intrathoracal desmoid tumour, with microscopically incomplete resection, was presented. The differential diagnosis, the therapeutic options and the ways of follow-up were discussed in detail.

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# Removal of a giant intrathoracic cyst from the anterior mediastinum

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## BACKGROUND

An intrathoracic mesothelial cyst is a congenital abnormality and represents 3-6% of mediastinal tumors[1,2]. These cysts are generally asymptomatic [3] and located in the anterior cardiophrenic angle[2,4], but can also be found in the paravertebral or paratracheal regions[2] or in the anterior mediastinum, as shown in this case.

**Case presentation:** A 45-year-old caucasian man with no significant past medical history was referred to our institution with progressive dyspnea. A chest X-ray showed a large mass in the anterior mediastinum (Figure 1A,B).

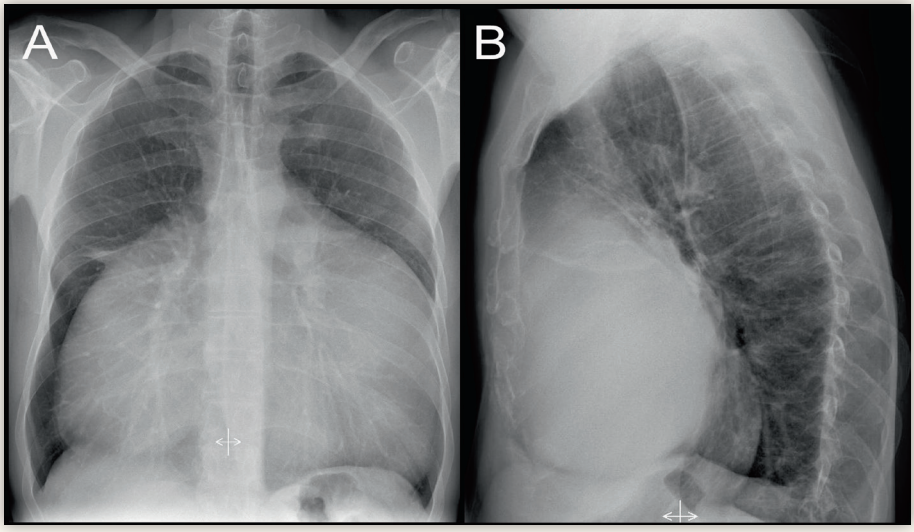


**Figure 1**. Preoperative posterioranterior **(A)** and lateral **(B)** chest X-ray showing a large mass in the anterior mediastinum with posterior displacement of the heart.

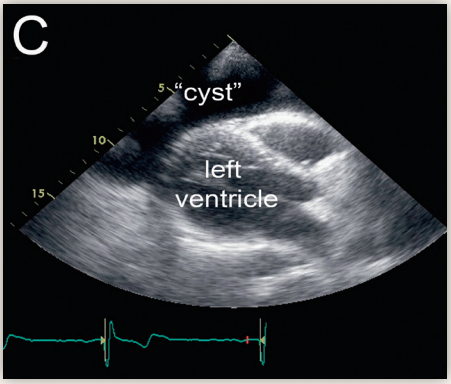


**Figure 1C.** Transthoracic echocardiography showing a large echolucent space around the heart (parasternal long-axis view).

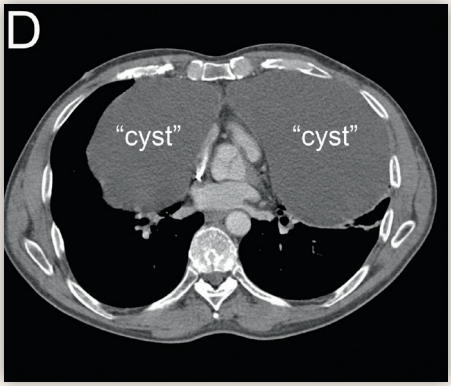


**Figure 1D.** Computed tomography showing a large cyst in the anterior mediastinum encasing the heart with compression of both lungs (transverse view at the level of the aortic valve).

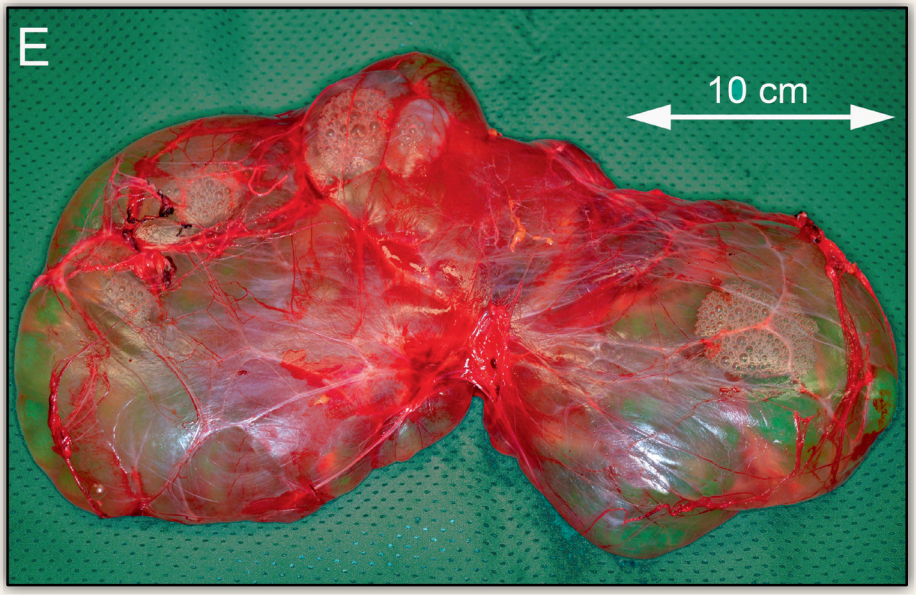


**Figure 1E.** Gross examination (E) revealed a thin-walled cyst filled with clear fluid.

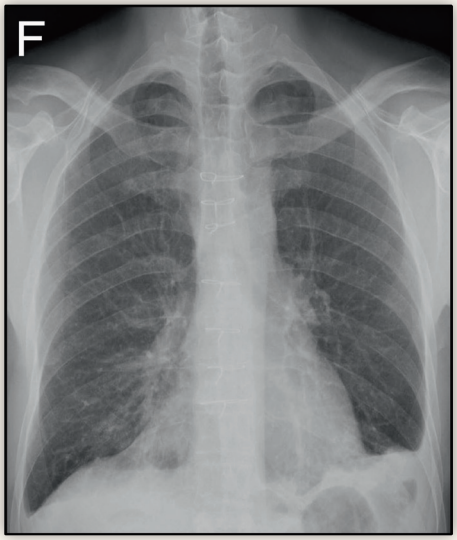


**Figure 1F.** A postoperative posterioranterior chest X-ray showed a remarkable improvement and a normal cardiac silhouette.

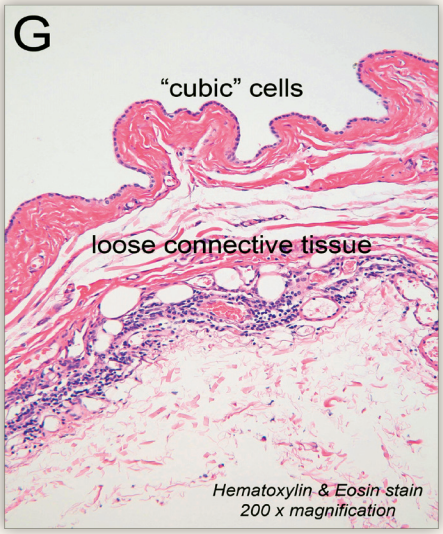


**Figure 1G.** Microscopic histopathologic examination showed a cyst wall lined by cubic cells and underlying loose connective tissue with remnants of thymic tissue.

Transthoracic echocardiography showed a large echolucent space around the heart (Figure 1C; parasternal long-axis view). Computertomography showed a large cyst in the anterior mediastinum encasing the heart (Figure 1D; transverse view at the level of the aortic valve). The cyst was 33 × 22 × 4 cm in size with a radiodensity of 12 to 18 Hounsfield units.

The patient chose to have the cyst removed due to its symptomatic nature and he underwent successful removal of the giant cyst through a median sternotomy. Due to the location and size of the cyst and in order to keep the cyst intact during resection, we were required to perform a median sternotomy. The cyst did not involve the pericardium or other surrounding structures. Only mild adhesions were encountered and the cyst was left intact during resection. The cyst was thin-walled and filled with clear fluid (Figure 1E). A postoperative chest X-ray showed a remarkable improvement and a normal cardiac silhouette (Figure 1F). Postoperative recovery was uneventful with resolution of the patient's symptoms.

Microscopic histopathologic examination (Figure 1G) showed a benign cyst (wall) lined by cubic cells and underlying loose connective tissue with remnants of thymic tissue. Although remnants of thymic tissue were found, the cyst did not seem to originate from the thymus, as thymic cysts are generally lined by (simple) squamous epithelium. The definitive diagnosis was an intrathoracic (simple) mesothelial cyst.

## DISCUSSION

An intrathoracic mesothelial (or "coelomic") cyst is a congenital abnormality. Little is known about the exact embryology, but mesothelial cysts are hypothesized to occur as a result of an anomaly in the development of the pericardial coelom[5]. Mesothelial cysts comprise 3-6% of mediastinal tumors and are usually diagnosed when patients are between 40 and 60 years of age[1,2]. An intrathoracic mesothelial cyst is a benign tumor that can become rather large before it becomes symptomatic.

The optimal management of intrathoracic mesothelial cysts is unknown. Due to its benign nature most asymptomatic cysts only require serial follow-up imaging[6]. Symptomatic cysts usually require treatment. Percutaneous ultrasound-guided or computed tomography-guided needle drainage of the cyst can be performed when symptoms are mild or if cytologic evaluation is required[4,7]. Cysts with more severe symptoms or complex cysts (irregular, multi-loculated, unusual location) require surgical resection[4]. Surgical resection can usually be performed with a limited thoracotomy or a videothoracoscopic procedure[2,8], but sometimes a median sternotomy may be required.

## Conclusions

An intrathoracic mesothelial cyst is a benign, generally asymptomatic tumor that can be located in the anterior cardiophrenic angle, the paravertebral or paratracheal regions, or in the anterior mediastinum. It can become rather large before it becomes symptomatic, at which point surgical removal is generally warranted.

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# Axillary Chest Wall Hibernoma with intrathoracic extension and presenting as Thoracic Outlet Syndrome

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## INTRODUCTION

Hibernomas are rare, slow-growing benign tumors originating from brown fat. The majority of cases occur in adults. Presenting as painless soft tissue masses which arise from the deeper layers of the body surface, they are easily confused with lipomas. Rarely, they occur in the chest wall, and if so, intra-thoracic extension is extremely rare. We present the imaging features of an axillary hibernoma with intra-thoracic extension, clinically presenting as TOS. The hibernoma was surgically removed.

## Case Report

A 55-year-old man was referred for a soft-tissue mass in his left axilla and clinical signs of TOS, with tingling in the right arm, hand and fingers which worsened with abduction of the right arm. In order to find a cause for the TOS, a routine chest-X-ray revealed a mass protruding into the apical portion of the left thoracic cavity on a chest X-ray (Figs. 1a and 1b ). The mass did not completely obscure the underlying lung and bones.

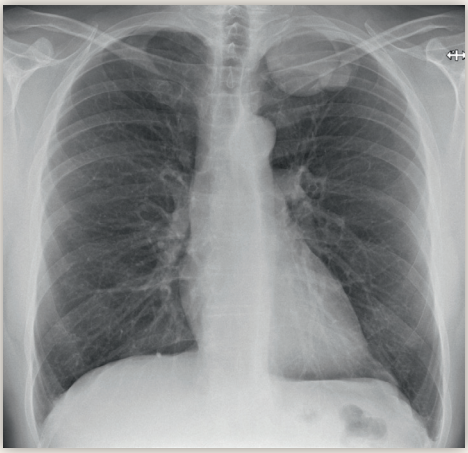

**Figure 1A.** Postero-anterior chest X-ray with tumor mass of intermediate density protruding into the apical portion of the left thoracic cavity .

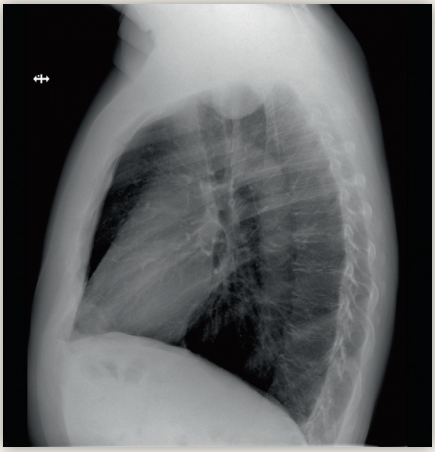

**Figure 1B.** Lateral view chest X-ray in which the apical tumor mass is partially obscured by the shoulder muscles .

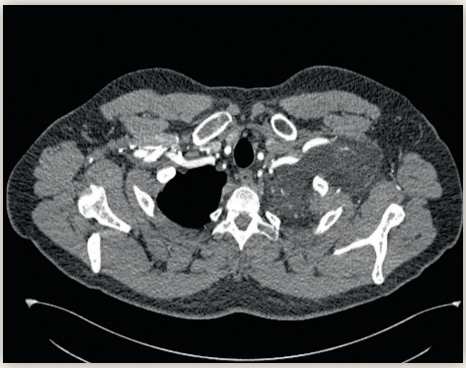

**Figure 2A.** Axial CT image at the level of the thoracic outlet, demonstrating the low attenuation mass and its feeding vessels originating from the extrathoracic part of the chest wall, protruding into the thoracic cavity.

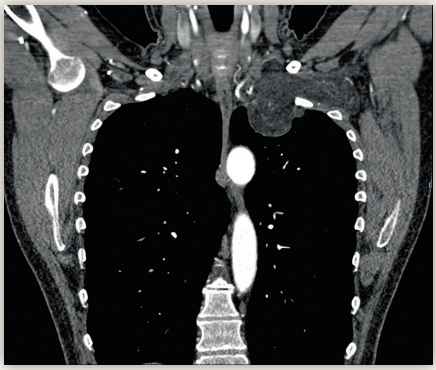

**Figure 2B.** Coronal reformat of the contrast-enhanced CT, demonstrating the hibernoma protruding into the thoracic cavity medial from the first rib on the left side.

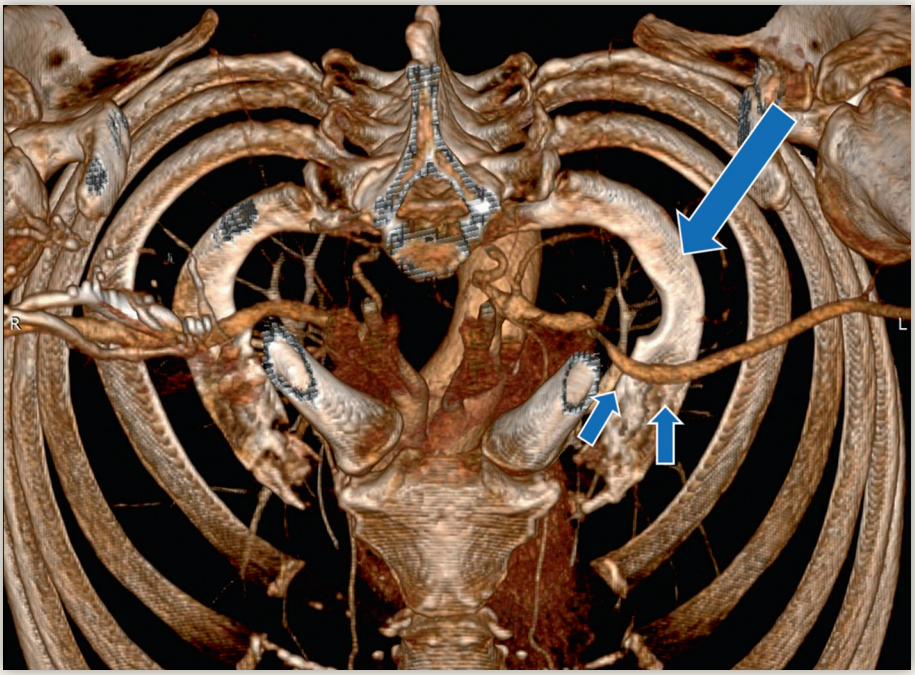


**Figure 2C.** 3D-reconstruction of the CT data, cranial view with the spine pointing upwards. Reconstruction parameters were tailored to visualize bone and contrast-filled vessels. Note the pressure erosion of the medial margin of the first rib (large arrow) and anterior displacement of the left subclavian artery (small arrows).

Next, for detailed anatomical information on the relation of the mass with the adjacent vascular and nervous structures, contrast enhanced Computed Tomography (CT) was ordered. This demonstrated a 9 x 7 cm low-density mass in the left axilla, overriding the first rib with extension into the left thoracic cavity (Figs. 2a and 2b ). Subsequently, surgery was performed in a single procedure with two steps. First, the extra-thoracic part of the hibernoma was approached by an axillar incision, similar as for removal of the first rib in TOS. The extra-thoracic part of the hibernoma was freed from the brachial plexus and subclavian vessels. In the second step the mass was freed bluntly from the pleura and thoracic wall by VATS. After mobilizing the intra-and extra-thoracic part of the tumor, the entire hibernoma was pulled into the thoracic cavity and removed with an Endobag™. The specimen was a 10 x 11 x 3 cm tan-brown colored, homogeneous tumor with the waist of the tumor at the former border between the extra-thoracic and intra-thoracic spaces still discernable (Fig. 4). 3D-reconstruction of the CT- data demonstrated anterior displacement of the subclavian vessels and pressure

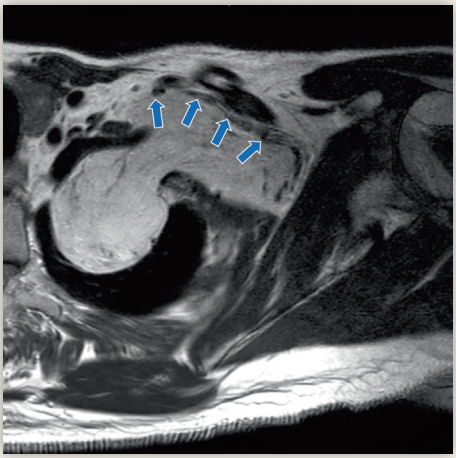

**Figure 3A.** T1-weighted transversal MRI, demonstrating the pedunculated high-signal (fatty) mass entering the apical part of the left chest cavity. Note the anterior displacement of the axillary plexus (small arrows) and the dumbbell shape of the mass.

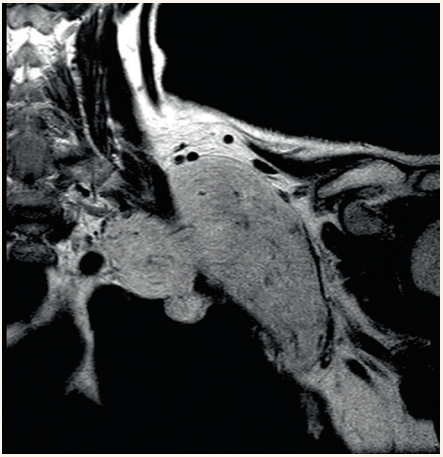

**Figure 3B.** (T1-weighted coronal MRI, demonstrating the dumbbell shape of the hibernoma.

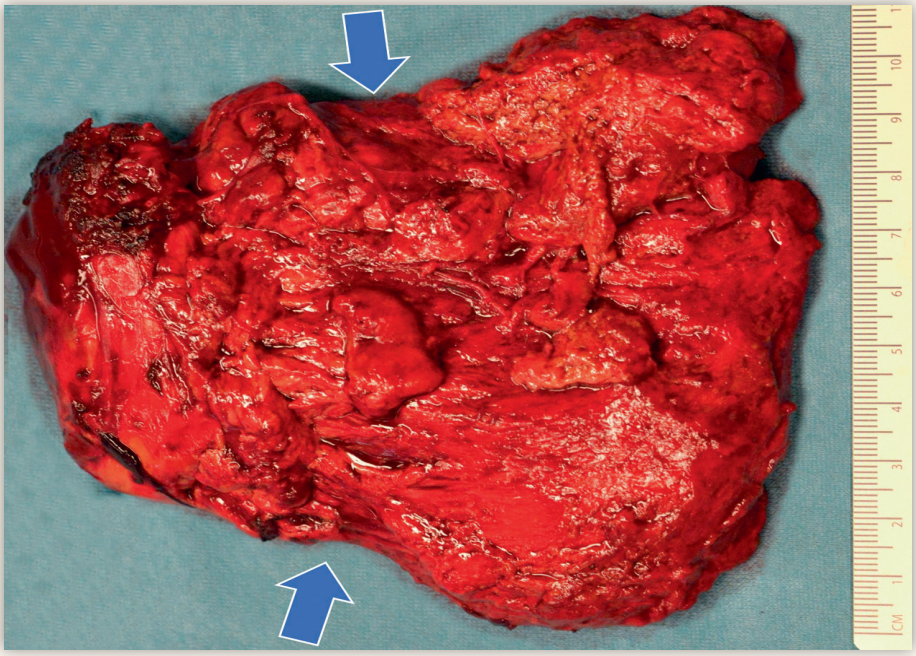

**Figure 4.** Anterior view of the resected hibernoma with the arrows indicating the waist of the tumor at the former border between the extra-thoracic and intra-thoracic spaces .

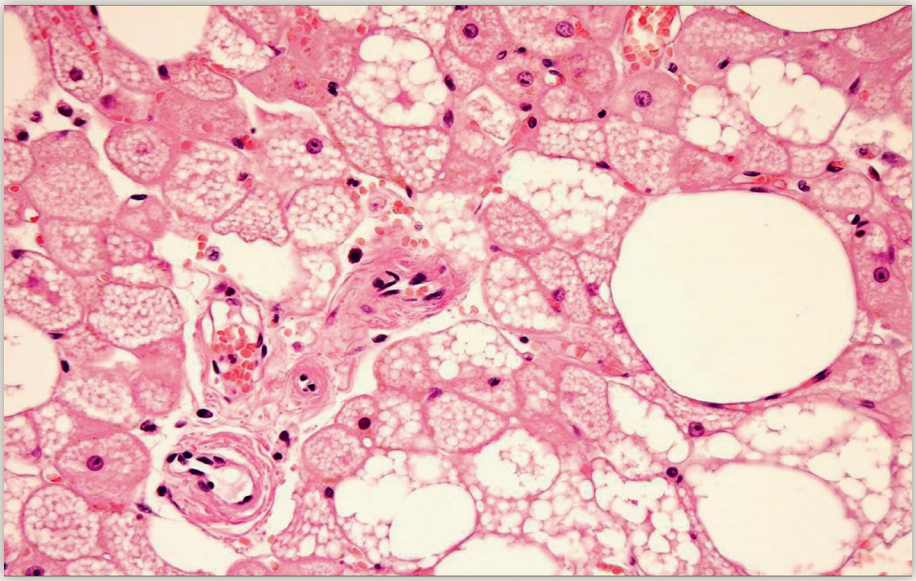

**Figure 5.** Photomicrograph of hibernoma consisting of multivacuolated tumor cells that resemble brown fat cells. (hematoxylin and eosin stain, original magnification x 400).

erosion of the inner margin of the first rib on the left side (Fig. 2c). Additional Magnetic Resonance Imaging (MRI) clearly demonstrated the dumbbell shape of the mass with distinct fatty signal characteristics and the anterior displacement of the axillary plexus (Figs. 3a and 3b). Histology of a needle-biopsy demonstrated hibernoma (details see below). Microscopic examination again showed features of hibernoma: brown fat cells with multivacuolated cytoplasm and central round nuclei (Fig. 5). On follow up, TOS disappeared with no signs of local tumor recurrence.

## DISCUSSION

Hibernomas are very rare soft-tissue tumors arising in fetal brown fat tissue and were first described by Merkel in 1906 [1]. Brown fat is believed to have a role in thermoregulation in human fetuses, and is therefore also called fetal lipoma [2]. Brown fat persists in the neck, axilla, mediastinum, periadrenal and perirenal areas and extremities. In a recent review on hibernomas, the most frequent site is the thigh [2]. Most cases of intra-thoracic hibernoma originate in the chest wall or mediastinum. The first route of expansive growth is mostly in the outward direction. Intra-thoracic expansion of an extra-thoracic hibernoma is extremely rare [2-4]. In our patient, the supra- and infraclavicular

septal linings together with the muscular alignment, prevented outward expansion of the hibernoma. Instead, inward growth occurred, as lung tissue offers little resistance against the growing mass. Slow growth allows the vascular system to adapt to the altered anatomical constellation. In our patient, this was demonstrated by the absence of functional vascular involvement, despite major anatomical displacement of the proximal vessels (Fig. 1D). TOS usually results from compression of the subclavian vessels as a result of narrowing of the costoclavicular space. Soft tissue neoplasms are rare causes for TOS [5].

Hibernomas have - to the best of our knowledge - never been described as a cause of TOS, most likely as a result of their plasticity and thus not causing pressure on adjacent anatomical structures. In that respect, our case is also unusual, as the growing mass in the relatively confined space of the axilla found a point of low resistance by entering through the upper chest aperture, where the intercostal muscles are absent. Continuous respiratory motion at the point of entry of the mass was most likely the cause for the pressure erosion of the inner margin of the first rib. MRI is the preferred imaging method for its superior capability to depict soft tissues masses and their adjacent vascular and skeletal structures [4]. In our case however, the pressure erosion of the first rib was noted on the CT only. As propranolol reduces 18F-FDG-uptake of (relatively hypermetabolic) brown fat tissue, staged PET-scan before and after oral administration of propranolol is advocated to differentiate hibernoma from lipoma and liposarcoma [6]. Malignant transformation or metastases have never been reported. In theory, necrosis could occur, although not documented. When left untreated, hibernomas continue to grow, leading to functional or cosmetic consequences and surgical excision can be considered. After complete excision, recurrence is absent and thus, the prognosis for patients is excellent.

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# Hybrid Bronchoscopic and Surgical Resection of Endotracheal Angiomatoid Fibrous Histiocytoma

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## INTRODUCTION

Angiomatoid fibrous histiocytoma (AFH) is a soft-tissue tumor that generally affects the extremities of children and young adults, but occasionally occurs at unusual locations such as the trachea [1-3]. This case-report demonstrates the challenge in making a correct (histological) diagnosis of endotracheal AFH and presents the first case of successful hybrid bronchoscopic and surgical resection of endotracheal AFH.

## Case Presentation

A 22-year-old female was referred with dyspnea and wheezing and an initial diagnosis of allergic asthma. Several weeks before she was admitted to the intensive care unit with acute respiratory failure due to a presumed severe asthma exacerbation. After weaning from mechanical ventilation she received formoterol and beclomethasone. Auscultation revealed pulmonary wheezing and a high-pitched stridor. Spirometry showed expiratory airflow obstruction and signs of severe fixed intrathoracic stenosis.

In retrospect, previous chest X-rays showed an intratracheal mass close to the carina (Figure 1A, blue arrow). Emergency computed tomography (CT) confirmed the presence of a large obstructing intratracheal mass (Figure 1B, blue arrow). Emergency bronchoscopy was performed under general anesthesia and revealed a large endotracheal tumor, blocking the airway almost completely (Figure 1C). Bronchoscopic debulking was performed using electrocautery and cryotherapy, leaving a patent airway with a small residual tumor (Figure 1D). The tumor was located 4 tracheal rings (approximately 2 centimeters) above the carina. Recovery was uneventful and the patient was discharged the next day without any remaining symptoms.

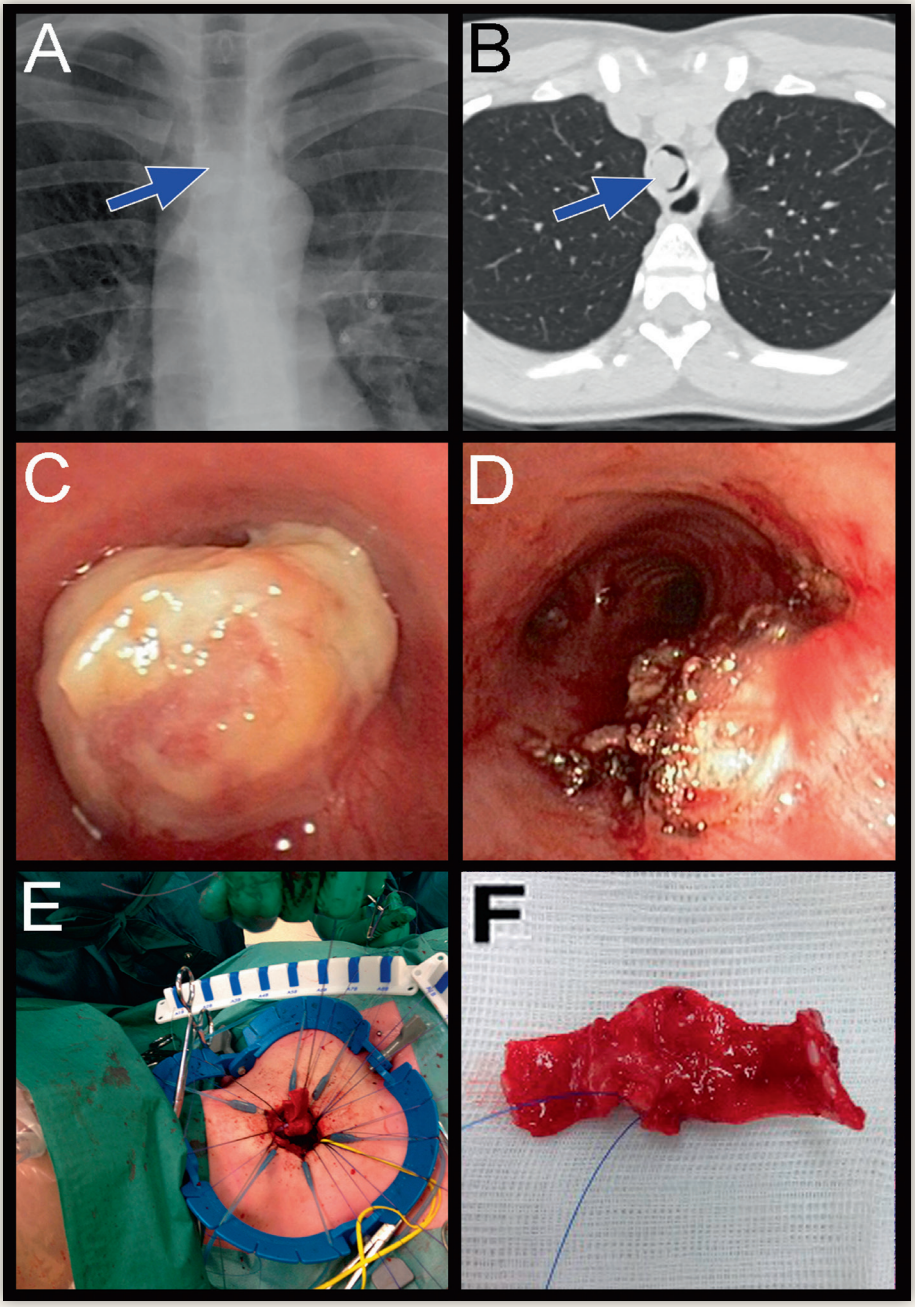


**Fig 1.** Explanation see text.

Histopathological examination showed an unclassifiable atypical myxoid spindle cell neoplasm with focal ALK expression and negative staining for keratins, EMA, TLE-1, p63, CD31, CD34, ERG, S100, SOX-10, TTF-1, SMA, desmin, myf4 and MUC4. Molecular analysis showed an EWSR1-CREB1 translocation, which can be found in primary pulmonary myxoid sarcoma (PPMS), AFH and in several other sarcomas. Under the working diagnosis of PPMS the patient underwent magnetic resonance imaging of both brain and kidneys and a whole body fluorodeoxyglucose positron emission tomography and CT. Both did not reveal any distant metastases.

The remaining tumor was removed through a cervical approach with a partial distal tracheal resection and end-to-end anastomosis with interrupted 4-0 PDS sutures (and two lateral interrupted 2-0 Vicryl sutures for approximation and anastomotic tension release) (Figure 1E, patient's head is left). The excised part of the trachea was cut open anteriorly and showed a tumor with a diameter of 15 mm located on the membranaceous portion (Figure 1F). High-frequency jet ventilation was used to allow temporal surgical interruption of the trachea. The patient was extubated immediately after the procedure. Recovery was uneventful and the patient was discharged three days after surgery. Microscopically, the tumor was removed completely.

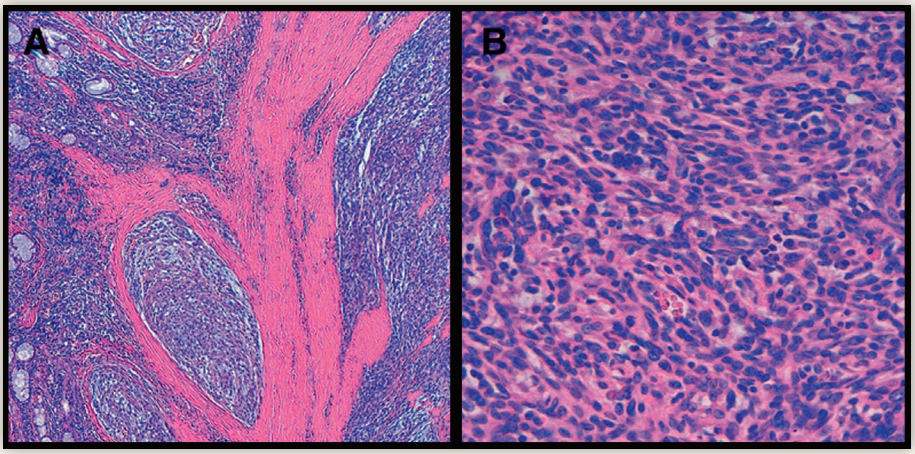


**Fig 2.** Explanation see text.

Histopathological examination at low power magnification showed distinct features of AFH with tumor nodules of variable size surrounded by a thick fibrous capsule with a rim of lymphoplasmacytic cells (Figure 2A). High power magnification showed solid tumor nodules composed of bland myoid spindle cells (Figure 2B). On follow-up, three years after surgery, the patient is asymptomatic, uses no asthma medication, has normal spirometry, and does not show any signs of recurrent tumor growth.

## DISCUSSION

AFH is a mesenchymal neoplasm of intermediate malignancy that generally affects children and young adults [1]. AFH occurs most commonly in the deep dermis or subcutis of extremities, followed by the trunk and head and neck [1]. AFH has a characteristic histological appearance simulating the appearance of a neoplasm occurring in a lymph node [1]. However, due to the variable histological appearance and the lack of consistently positive immunohistochemical markers, the diagnosis can be difficult [1]. Molecular genetic studies have shown three characteristic translocations and nearly 93% of AFH have a rearrangement of ESWR1 (often a EWSR1-CREB1 translocation), which is of diagnostic relevance [1]. However, the EWSR1-CREB1 translocation is also described in other tumors, such as PPMS [1,4]. Although PPMS and AFH may represent an overlapping histologic spectrum, PPMS is consistently negative for desmin and characterized by a predominately reticular architecture and absence of a lymphoplasmacytic cuff [1,4]. This case-report confirms the challenge in making a correct (histological) diagnosis of AFH, especially when it occurs at an unusual site.

There is one previous case report that describes endobronchial AFH in two cases [2] and only one case report that describes (upper) endotracheal AFH [3]. To our knowledge, surgical resection of endotracheal AFH has not been described before, nor has a hybrid bronchoscopic and surgical resection strategy. A staged resection was required in this case to quickly secure the airway, allowing a lower-risk planned surgical procedure for complete resection. We chose a cervical approach, instead of a more invasive, painful and cosmetically less satisfying thoracotomy. Although a thoracotomy is generally recommended for distal tracheal resections, we have shown that distal tracheal resection for endotracheal AFH can be safely performed through a cervical approach with excellent follow-up results.

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# DISCUSSION AND FUTURE PERSPECTIVES

The success of surgery in oncology can be regarded as the ultimate tumor reduction therapy. It is the result of a technically feasible surgical approach and the functional condition of the patient. In non-metastatic disease, complete resection with clear margins should be the goal, but whether a complete resection can be achieved, is dependent on the extent of tumor growth and the involvement of vital organs. The skills and experience of the surgeon are important in determining to which extent surgery will be possible. Therefore, the stage of the tumor and the experience of the surgeon dictate the surgical spectrum of oncological procedures and operations. Simultaneously, patient related restrictions (PRR) can impede the outcome of surgery and thereby limit the ultimate success. We investigated whether PRR and the experience of the surgeon influence the success of mediastinoscopy in staging the mediastinum in lung cancer. Experience means having knowledge of the usual course of events, obtained through observation and proper skills. The term 'experience' is almost synonymous with 'insight', 'know-how' and 'knowing', but it can also mean skillful. A person with considerable experience in a certain area is called an 'expert' and his experience is called 'expertise'. In our study the experience and 'expertise' of the surgeon significantly influenced the success of the mediastinoscopy. This means that mediastinoscopy is best performed by experienced surgeons. PRR proved to be an even stronger predictor for the success of mediastinoscopy, although in a negative way. When PRR were present, it was no longer relevant whether the procedure was performed by an experienced or less experienced surgeon. PRR hindered the execution of the procedure in such a way, that even an experienced surgeon was unsuccessful. Our study did have some limitations. It was a retrospective study with a long time frame. One should consider the outcomes of this study in that perspective. Another limitation is that the diagnostic value of procedures such as mediastinoscopy and probably also of EBUS-TBNA/EUS-FNA (EndoBronchial UltraSound-guided TransBronchial Needle Aspiration and Endoesophageal UltraSound Fine Needle Aspiration), depends on how they are technically performed [1]. Numbers matter when the experience or 'expertise' of the surgeon dictates the success of the mediastinoscopy. Therefore, the decreasing numbers of mediastinoscopies can have a negative effect on the success of the mediastinoscopy itself. Especially now that the EBUS and EUS appear to be strong 'competitors' in mediastinal staging of lung cancer. EBUS and EUS have high sensitivity, high specificity, are less invasive and have less complications [2]. Therefore, it seems almost inevitable that the number of mediastinoscopies in mediastinal staging will decrease. The MEDIASTrial may demonstrate

whether we can omit mediastinoscopy in the staging of the mediastinum in lung cancer, even with a negative EBUS and EUS [3]. Does this scenario mean the end of the mediastinoscopy? No way! Up till now we are talking about EBUS, EUS and mediastinoscopy as procedures for staging the mediastinum. Often these procedures are also used for a diagnosis. However, a diagnosis is preferably made on tumor tissue and not on individual cells; histology, rather than cytology. Histology is important to have a view on tumor cells, tumor architecture and tumor microenvironment. Histology also provides estimates of lymphocyte influx. Furthermore, sufficient quantities of tumor cells are needed for detection of molecular abnormalities. Nowadays PD-L1 expression and the detection of HLA abnormalities are important in the era of immunotherapy. Increasing numbers of biomarkers are used at the pathology department to increase chances for successful immunotherapy. With current developments in DNA diagnostics, more information will come available for making selections in immunotherapy and targeted therapy [4-7]. However, DNA diagnostics are only reliable when sufficient histological material is available. The abovementioned implies that biopsy samples must provide enough tissue to fulfill such requirements. As EBUS/EUS aspirations or biopsies are small, in general they cannot supply adequate amounts of tissue and this gives new opportunities to mediastinoscopy [8]. Another diagnostic challenge comes along with better CT scanning where we can detect smaller relevant lung nodules. Lung cancer screening protocols - such as the NELSON protocol - defines criteria for lung nodules that are suspect for malignancy [9,10]. This depends on radiologically assessed volume size and growth (nodule doubling time). However, only about 40% of the nodules that fulfill those criteria, are malignant. Therefore, we looked into minimal invasive surgery and procedures to locate such small nodules. The application of hookwires – similar to their use in breast surgery - proved to be a success. The combination of CT-guided Percutaneous Hookwire Localization (CT-PHL) of small pulmonary nodules followed by wedge resection by Video Assisted Thoracic Surgery (VATS) reduced VATS time, and decreased conversion to thoracotomy. It also showed a very high diagnostic accuracy and therapeutic efficacy. Furthermore, diagnosis and therapy were performed in a single procedure. For unknown reasons, this procedure -performed in collaboration with the interventional radiologist- is yet still scarcely used in other hospitals. CT-PHL will always remain a technique which uses ionizing radiation. Hardware as well as software developments continue to decrease radiation exposure, resulting in dedicated low-dose lung nodule detection protocols which are currently used for screening protocols [9,10]. The radiation exposure during CT-guided hookwire insertion is directly related to the experience of the interventional radiologist who is performing the procedure. In addition, patient related restrictions also apply in radiological procedures, similarly

to mediastinoscopy and VATS. Other localization techniques are being developed. Electromagnetic navigational bronchoscopy is a localization technique which yields high success percentages, equal to CT-PHL. It does not use ionizing radiation and it has the (theoretical) advantage that the waiting time between bronchoscopy and resection is shorter than when CT is employed [11]. Similarly, cone beam CT is used to localize pulmonary nodules with local injection of lipiodol, followed by VATS in combination with fluoroscopy. The success rate of such studies is as high as in our CT-PHL study. The VATS-fluoroscopy combination however, is probably more complex as data on the duration of the VATS are lacking [12]. Screening protocols are increasingly employed and the increased life expectancy of generations to come will lead to more metastatic lung disease [9,10]. These two factors lead to increased detection of unspecified lung nodules necessitating adequate tissue diagnosis and the number of patients requiring such procedures will be overwhelming. Therefore, tailored diagnostic pathways have to be initiated, followed by tailored treatment protocols, either through surgery, radiotherapy, chemotherapy, immunotherapy, or combined. Centralization of surgical care is once again, of utmost importance for optimal treatment. For this moment, CT-PHL prior to VATS wedge resection for pulmonary nodules seems to be a very efficient and safe procedure.

This also applies to oligometastatic disease of the lungs. The surgical treatment of oligometastases in the lung (Pulmonary MEtastasectomy (PME)) has been considered potentially curative over the past decades. However, evidence is very weak [13,14]. With Stereotactic ABlative Radiotherapy (SABR) a new non-invasive treatment was introduced to eradicate small volume solid tumors in the lung. Despite this development more than 20 years ago, SABR is still only reserved for patients who cannot undergo surgery. Proof that surgery gives a better survival or disease-free interval in comparison with SABR does not exist. In both our short-term and long-term cohort study, we also were unable to demonstrate significantly better survival in the group that underwent PME. It should be noted that these are all retrospective studies. Both PME and SABR are considered potentially curative treatments, when all oligometastases in the lung have been eradicated. Although in our studies PME and SABR did not differ in terms of survival, the future perspective can be different. A major shortcoming of SABR with respect to surgery is the lack of sufficient histological material. On the other hand, a limited resection of just one metastasis can give histopathological clarity, DNA diagnosis, and –with that- access to personalized therapy. This makes resection of sufficient tumor tissue -either mediastinal or pulmonary- an important link to immunotherapy and targeted therapy. Where there is no proof that surgery of oligometastases of the lung gives a better survival or disease-free interval in comparison with SABR, how different that is

for early stage resectable Non-Small Cell Lung Cancer (NSCLC). Surgery, in general lobectomy, is still the gold standard in the treatment of stage I NSCLC [15]. In our study, we compared SABR and surgery in the treatment of stage I NSCLC. SABR had worse locoregional tumor control compared with surgery which confirms earlier reports [16]. The rapid development of DNA diagnostics, immunotherapy and targeted therapy can have a major impact on the treatment of NSCLC in general and more specific on stage I NSCLC. Consequently, this perspective may also alter future surgical approaches; instead of a lobectomy, a segmentectomy via VATS will give sufficient material for DNA diagnostics and adequate immunotherapy. 'Segmentectomy' instead of 'lobectomy' may become the new gold standard in the immunotherapy era [17]. Developments in diagnostic techniques are continuously evolving. Simultaneously, the therapeutic spectrum is spectacularly expanding. This leads to increased need of representative tissue samples.

This thesis emphasizes, that the above-mentioned diagnostic strategies and surgical procedures in the treatment of thoracic tumors, are the result of a multidisciplinary consultation that should result in a single comprehensive advice to the patient.

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# Summary



This thesis provides an overview of diagnostic and therapeutic strategies in the multidisciplinary treatment of lung carcinoma and thoracic neoplasms. The collaboration between the disciplines thoracic surgery, radiotherapy and interventional radiology is emphasized.

**CHAPTER 1**
In the first chapter we described the research questions and hypotheses as well as the set-up of the thesis.

**CHAPTER 2**
Quality comes with quantity and a surgical technically "difficult" patient has a lower chance of a successful treatment than a surgical technically "easy" patient. This sounds logical, but is difficult to prove. In chapter 2 we have investigated whether the success of the staging of lung cancer with cervical mediastinoscopy was dependent on surgical experience. In the same study we studied the influence of patient related restrictions on the staging success of mediastinoscopy. Both factors proved to be good, and independent predictors for the success of cervical mediastinoscopy. Experience and skills of the operator appeared to be related to the number of cervical mediastinoscopies performed and with that, with the expertise of the operator. For the cervical mediastinoscopy the adagium was, "the greater the experience and skills the larger the success". However, this adagium does not apply, when patient related restrictions make the procedure more difficult or even impossible. In the latter case, greater experience and skills of the operator no longer contributed to a better outcome of the procedure. Since mediastinal lymph node staging is crucial for the treatment and outcome of lung cancer, we advocate cervical mediastinoscopy to be performed and taught by experienced operators only.

**CHAPTER 3**
In chapter 3 we describe the 'rise and fall' of cervical mediastinoscopy with a brief historical overview of how initially the procedure developed and what is the current status of cervical mediastinoscopy. Mediastinal lymph node staging is crucial for the choice of treatment and the outcome of the patient with lung cancer. With the emergence of minimal invasive ultrasound-guided transbronchial (EBUS) and trans-esophageal (EUS) lymph node staging of the mediastinum in lung cancer, the number of cervical mediastinoscopies decreases. The MEDIASTrial will have to determine whether there is still room for the cervical mediastinoscopy in the staging of the mediastinum. The thoracic surgery community must be aware of these developments and should consider the possibility of new indications for mediastinoscopy. One possibility may be that more tumor tissue is needed for new DNA diagnostics.

This applies not only for genomic analysis, but also for histology instead of cytology for predictions in immunotherapy and targeted therapy. That means that more tumor tissue is needed to provide maximum opportunity for adequate treatment. The current ultrasound guided needle aspirations EBUS and EUS techniques are suitable for staging but - due to limited sample size - are far less suitable for good initial (molecular) diagnostics. After more than sixty valuable years, the heydays for the old indications of cervical mediastinoscopy seem to have passed. The role of cervical mediastinoscopy in the investigation of the upper mediastinum and its role in staging in lung cancer have to be redefined.

**CHAPTER 4**

Given the current developments in lung cancer screening (the US National Lung Screening Trial and the European NELSON study) in high risk groups, it is to be expected that more small lung nodules (<1 cm) will be found. Smokers are at high-risk for lung cancer. In South-East Asia, air pollution and the 'smoking' kitchen stoves are also important risk factors for the development of lung cancer. What to do with these small lung nodules? In the above-mentioned studies screening is used in asymptomatic patients with a high risk of lung malignancy. Therefore, early tissue diagnosis is crucial. The retrospective study in chapter 4 proved that 'CT-guided hookwire localization' VATS (Video Assisted Thoracic Surgery) was a safe and highly reliable method to locate, and subsequently remove these small nodules during surgery. As a result, VATS took less time with reduced chance for extension to major surgery, i.e. thoracotomy. Based on the findings of our study, we now recommend CT guided hookwire localization and VATS not only in screening studies, but also for the identification of oligometastases in the lung that are eligible for possible resection.

**CHAPTER 5**

In chapter 5 we retrospectively compared pulmonary metastasectomy (PME) and stereotactic ablative radiotherapy (SABR) in patients with oligometastases in the lungs with regard to survival. The standard treatment is PME. In case PME was not an option, patients were treated with SABR. That approach led to a detrimental selection bias towards SABR. Our study showed that the survival of patients treated with PME was not significantly better than patients treated with SABR. Due to the retrospective nature of this study, patient selection, clinical presentation and differences in tumor biology, a definitive statement on the best treatment is not possible without prospective studies.

**CHAPTER 6**
SABR is still regarded as the first choice of treatment for patients with oligometastasis in the lung who are not eligible for surgery. Randomized or prospective cohort studies comparing PME and SABR in the treatment of pulmonary oligometastases do not exist. Chapter 6 presents the differences in long-term survival of patients with 1 to 5 oligometastases in the lung treated with PME or with SABR. Even after a minimum 6-year follow-up of our patient cohort and a re-analysis of previous data, there was no evidence that surgical resection of lung oligometastases provides better survival or local control than does stereotactic radiotherapy. This finding persisted despite the higher age and the shorter metastasis-free interval in the SABR group, which could be associated with a greater risk of death. The resulting question is then, for which indications the respective treatments can be used when a clear survival difference is absent. If it is important - from a differential diagnostic point of view - to know which tumor is involved and if systemic treatment is indicated, then a wedge resection can produce material for tissue diagnostics and mutation analysis.

**CHAPTER 7**
In chapter 7 the overall survival and probability of a tumor recurrence was analyzed in patients with clinical stage I non-small cell lung carcinoma (NSCLC) treated with surgery or with SABR. The patient characteristics in this study showed that patients treated with surgery were on average 10 years younger, fitter, and had fewer additional comorbidities as compared to the group treated with SABR. However, the corrected overall survival between surgery and SABR proved to be the same. SABR gave worse locoregional control of the lymph nodes when compared to surgery. Nevertheless, SABR proved to be an excellent treatment for patients with stage I lung cancer who were not fit enough to undergo surgery.

**CHAPTER 8**
The surgical palette of the cardiothoracic surgeon consists largely of ‘routine’ procedures, and the work is strongly fixed in protocols. All surgery starts with a well-thought-out plan. This applies to both ‘rare’ and ‘routine’ surgery. After all, ‘when the first brick is not placed right, the whole house collapses’. Chapter 8 is a balanced selection of exceptional case histories and represents the borderlands of thoracic neoplasms, both malignant and benign. These case studies illustrate and emphasize the reasons for which surgery should always start with a solid strategy.

**CHAPTER 9**

In chapter 9 the diagnostic strategies and surgical procedures for thoracic tumors - as investigated and described in this thesis - are discussed, and the surgical future perspectives in the treatment are outlined. Future expectations are depicted against a changing clinical background with challenging new surgical techniques and promising developments in molecular biology.

# Samenvatting



Dit proefschrift geeft een overzicht van diagnostische en therapeutische strategieën in de multidisciplinaire behandeling van nieuwvormingen in de thorax. De nadruk ligt op de samenwerking van de disciplines thoraxchirurgie, radiotherapie en interventie radiologie.

**HOOFDSTUK 1**
Het eerste hoofdstuk beschrijft de aanleiding, de formulering van de onderzoekshypothesen en de opzet van het proefschrift.

**HOOFDSTUK 2**
Kwaliteit komt met kwantiteit en een chirurgisch technisch "moeilijke" patiënt heeft een lagere kans op een succesvolle behandeling dan een chirurgisch technisch "makkelijke" patiënt. Dat klinkt logisch, maar is lastig te bewijzen. In hoofdstuk 2 hebben we onderzocht of het succes van de stadiëring van longkanker met cervicale mediastinoscopie afhankelijk was van chirurgische ervaring. In dezelfde studie werd eveneens onderzocht wat de invloed was van patiënt gerelateerde beperkingen op het succes van de stadiëring middels mediastinoscopie. Beide factoren bleken goede, en onafhankelijke voorspellers te zijn voor het succes van de cervicale mediastinoscopie. Ervaring en vaardigheid van de operateur bleken samen te hangen met het aantal verrichte cervicale mediastinoscopieën en daarmee, met de expertise van de operateur. Voor de cervicale mediastinoscopie gold, "hoe groter de ervaring en vaardigheid hoe groter het succes". Deze stelling bleek echter niet op te gaan wanneer patiënt gerelateerde beperkingen de procedure bemoeilijken, dan wel onmogelijk maken. In het laatste geval droeg een grotere ervaring en vaardigheid van de operateur niet meer bij aan een betere uitkomst van de procedure. Omdat mediastinale lymfeklier stadiëring cruciaal is voor de behandeling en uitkomst van longkanker, stellen wij dat de cervicale mediastinoscopie uitsluitend zou moeten worden uitgevoerd en onderwezen door ervaren operateurs.

**HOOFDSTUK 3**
In hoofdstuk 3 wordt de 'opkomst en ondergang' van de cervicale mediastinoscopie beschreven met een kort overzicht van hoe het begon en waar de cervicale mediastinoscopie nu staat. Mediastinale lymfeklier stadiëring is cruciaal voor de keuze van behandeling en de uitkomst van de patiënt met longkanker. Met de opkomst van de minimaal invasieve echografisch geleide transbronchiale (EBUS) en trans-oesophageale (EUS) lymfklierstadiëring van het mediastinum bij longkanker, vermindert het aantal cervicale mediastinoscopieën. De MEDIASTrial zal uitsluitsel moeten geven of er nog plaats is voor de cervicale mediastinscopie bij de stadiëring van het mediastinum. De thoraxchirurgische gemeenschap moet zich bewust

zijn van deze ontwikkelingen en zou moeten nadenken over de mogelijkheid van nieuwe indicaties voor de mediastinoscopie. Eén mogelijkheid kan zijn dat bij de nieuwe DNA-diagnostiek meer tumorweefsel nodig is voor voorspellingen in de immunotherapie. Dat betekent dat er meer tumorweefsel nodig is om de kansen voor adequate behandeling te vergroten. De huidige echografisch geleide naaldpuncties middels EBUS en EUS zijn geschikt voor stadiëring maar - door de geringe weefselhoeveelheid - veel minder geschikt voor een goede initiële (moleculaire) diagnostiek. Na meer dan zestig waardevolle jaren lijken de hoogtijdagen van de cervicale mediastinoscopie voor de oude indicaties voorbij. De rol van de cervicale mediastinoscopie in het onderzoek van het bovenste mediastinum en de rol in de stadiëring bij longkanker moet opnieuw worden bepaald.

**HOOFDSTUK 4**
Gezien de huidige ontwikkelingen rond longkanker screening (de Amerikaanse National Lung Screening Trial en de Europese NELSON-studie) in hoog risicogroepen is de verwachting dat er meer kleine longnodules (< 1cm) zullen worden gevonden. Rokers zijn een hoog risicogroep voor het krijgen van longkanker. In Zuidoost-Azië zijn luchtvervuiling en de 'rokende' keuken ook belangrijke risicofactoren voor het ontstaan van longkanker. Wat te doen met deze kleine long nodules? In bovenstaande studies betreft het de screening van asymptomatische patiënten met een hoog risico op longmaligniteit. Daarom is vroege weefseldiagnose cruciaal. De retrospectieve studie in hoofdstuk 4 bewees dat 'CT draadgeleide VATS' (Video Assisted Thoracic Surgery) een veilige en zeer betrouwbare methode bleek te zijn om kleine nodules in de long tijdens de operatie te lokaliseren en chirurgisch te verwijderen. Daardoor nam de VATS minder tijd en werd de kans op een uitbreiding van de operatie naar een grotere, en meer invasieve thoracotomie sterk verkleind. Op basis van de bevindingen van deze studie kunnen wij nu CT draadgeleide VATS niet alleen aanbevelen in screening-studies, maar ook bij de diagnostiek van oligometastasen in de long die in aanmerking komen voor eventuele resectie.

**HOOFDSTUK 5**
In hoofdstuk 5 vergeleken we retrospectief de chirurgische en radiotherapeutische behandeling van patiënten met oligometastasen in de longen voor wat betreft de overleving. De standaardbehandeling van eerste keuze was pulmonale metastasectomie (PME). Wanneer chirurgische metastasectomie geen behandelkeuze was, werden patiënten behandeld met stereotactische ablatieve radiotherapie (SABR). Dat bleek een selectie bias te

geven ten nadele van de behandeling met SABR. Uit onze studie kwam naar voren dat de overleving van de patiënten behandeld met PME niet significant hoger was dan de overleving van patiënten behandeld met SABR. Als gevolg van het retrospectieve karakter van deze studie, de patiënt selectie, de klinische presentatie en het brede scala aan verschillen in tumorbiologie, bleek een definitieve uitspraak niet mogelijk zonder prospectieve studies.

**HOOFDSTUK 6**
SABR wordt nog steeds beschouwd als de eerste behandelkeuze voor patiënten met oligometastasen in de long die niet in aanmerking komen voor chirurgisch ingrijpen. Gerandomiseerde of prospectieve cohortstudies waarin PME en SABR worden vergeleken in de behandeling van long oligometastasen bestaan niet. In hoofdstuk 6 werden de verschillen in de lange termijn overleving gepresenteerd van patiënten met 1 tot 5 oligometastasen in de long die werden behandeld met PME of met SABR. Zelfs na een minimale follow-up van 6 jaar van ons patiënten cohort en een re-analyse van de eerdere gegevens, bleek er geen bewijs te bestaan dat resectie van oligometastasen van de long een betere overleving of lokale controle geeft dan stereotactische radiotherapie. Deze bevinding bleef bestaan ondanks de hogere leeftijd en het kortere metastase-vrije interval in de SABR-groep, hetgeen gepaard zou kunnen gaan met een grotere kans op overlijden. De daaruit voortvloeiende vraag is dan voor welke indicaties de respectievelijke behandelingen ingezet kunnen worden als er geen duidelijk overlevingsverschil tussen beide behandelingen bestaat. Als het uit differentiaal diagnostisch oogpunt belangrijk is om te weten om welke tumor het gaat en of systemische behandeling zin heeft, dan kan een wigresectie materiaal opleveren voor weefseldiagnostiek en mutatie analyse.

**HOOFDSTUK 7**
In hoofdstuk 7 werd de algehele overleving en de kans op een tumorrecidief geanalyseerd in patiënten met klinisch stadium I niet-kleincellig longcarcinoom (NSCLC) die werden behandeld met PME of met SABR. De patiënt karakteristieken in deze studie demonstreerden dat patiënten die werden behandeld met chirurgie gemiddeld 10 jaar jonger en fitter waren, en minder bijkomende ziekten hadden in vergelijking met de groep die werd behandeld met SABR. Desondanks bleek de gecorrigeerde totale overleving tussen chirurgie en SABR gelijk. SABR gaf een slechtere locoregionale controle van de lymfeklieren in vergelijking met chirurgie, maar bleek een prima behandeling te zijn voor patiënten met stadium I longkanker die niet fit genoeg waren om een operatie te ondergaan.

**HOOFDSTUK 8**
Het operatie-palet van de cardiothoracaal chirurg bestaat grotendeels uit ‘routine’ procedures waar sterk geprotocolleerd wordt gewerkt. Iedere operatie begint met een goed doordacht plan. Dat geldt voor zowel de ‘zeldzame’ als voor de ‘routine’ operaties. Immers, ‘wanneer de eerste steen niet goed ligt, stort het hele huis in elkaar’. Hoofdstuk 8 is een gebalanceerde selectie van uitzonderlijke casuïstiek en representeert de grensgebieden van nieuwvormingen in de thorax, zowel kwaad- als goedaardig. Deze casuïstiek illustreert en benadrukt waarom chirurgie altijd moet beginnen met een solide strategie.

**HOOFDSTUK 9**
In hoofdstuk 9 worden de diagnostische strategieën en chirurgische procedures voor thoracale tumoren - zoals onderzocht en beschreven in dit proefschrift - bediscussieerd en worden chirurgische toekomstperspectieven geschetst in de multidisciplinaire behandeling. De toekomstverwachtingen worden geschetst in een sterk veranderend werkveld waarin nieuwe chirurgisch technische en moleculairbiologische methodes een grote rol gaan spelen.

## Curriculum Vitae

De auteur van dit proefschrift studeerde, na het behalen van het eindexamen VWO, geneeskunde aan de Rijksuniversiteit Utrecht. Belangstelling voor de cardio-thoracale chirurgie ontstond tijdens zijn co-assistentschap heelkunde. Na het behalen van zijn artsexamen werkte hij als assistent-niet-in-opleiding achtereenvolgens op de afdeling cardio-thoracale chirurgie van het St. Antonius Ziekenhuis in Nieuwegein (hoofd: F.E.E. Vermeulen) en de afdeling cardio-thoracale chirurgie van het Radboud Universitair Medisch Centrum in Nijmegen (hoofd: Prof. dr. L.K. Lacquet).
Na aanvang van zijn opleiding tot cardio-thoracaal chirurg werkte hij twee jaar als assistent algemene chirurgie in het Rijnstate Ziekenhuis in Arnhem (opleider: Dr. W.F. Eggink) en vervolgens als assistent cardio-thoracale chirurgie in het Radboud Universitair Medisch Centrum in Nijmegen (opleider: Prof. dr. L.K. Lacquet) en het St. Antonius Ziekenhuis in Nieuwegein (opleider: Dr. A. Brutel de la Rivière). Na zijn registratie als cardio-thoracaal chirurg werkt hij als staflid cardio-thoracale chirurgie in het Universitair Medisch Centrum Groningen.

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